MEDICAL AND SURGICAL REPORT

OF THE

PRESBYTERIAN HOSPITAL

IN THE

CITY OF NEW YORK.

VOLUME VIII
DECEMBER, 1908

EDITED BY

JOHN S. THACHER, M.D.
GEORGE WOOLSEY, M.D.

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JOHN S. THACHER, M.D.
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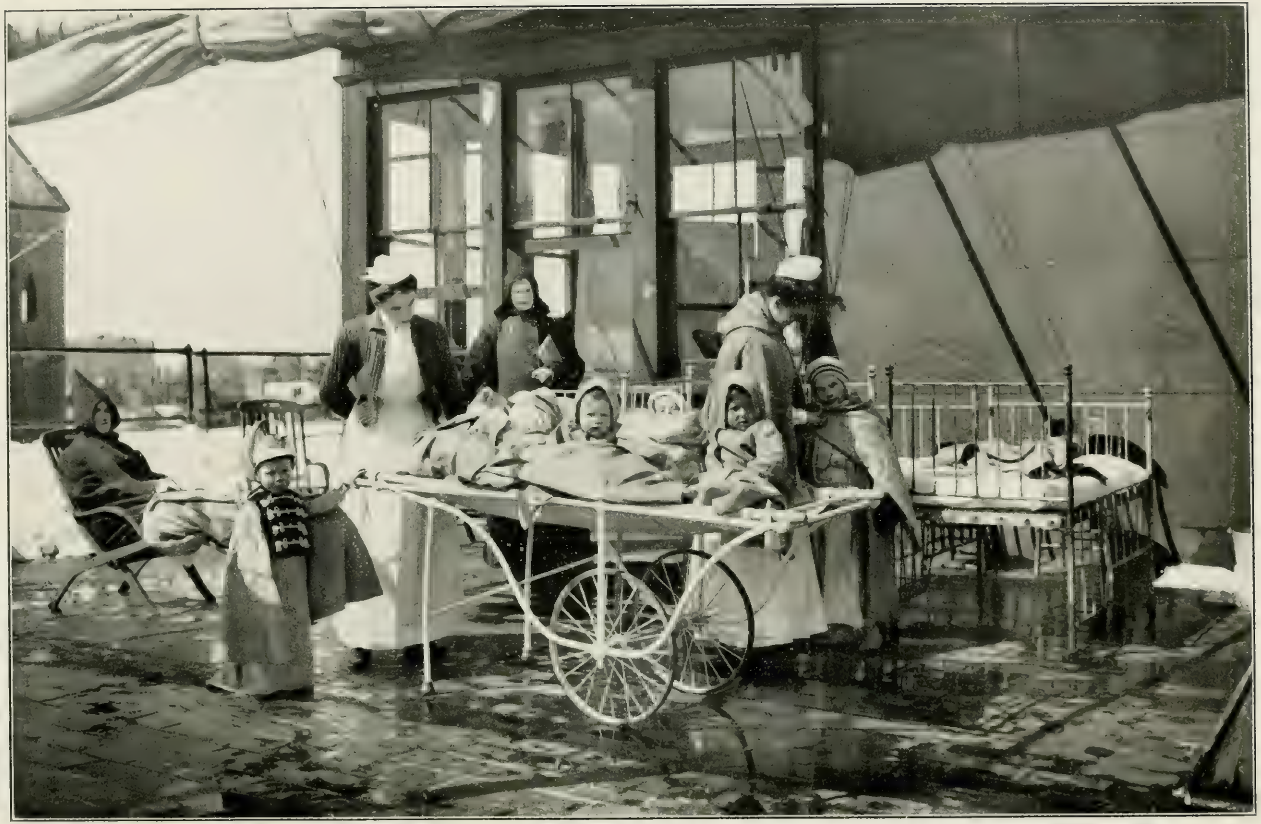


FIG. 1—"UNIMPROVED" ROOF. FIRST ATTEMPT AT REGULAR OPEN AIR TREATMENT

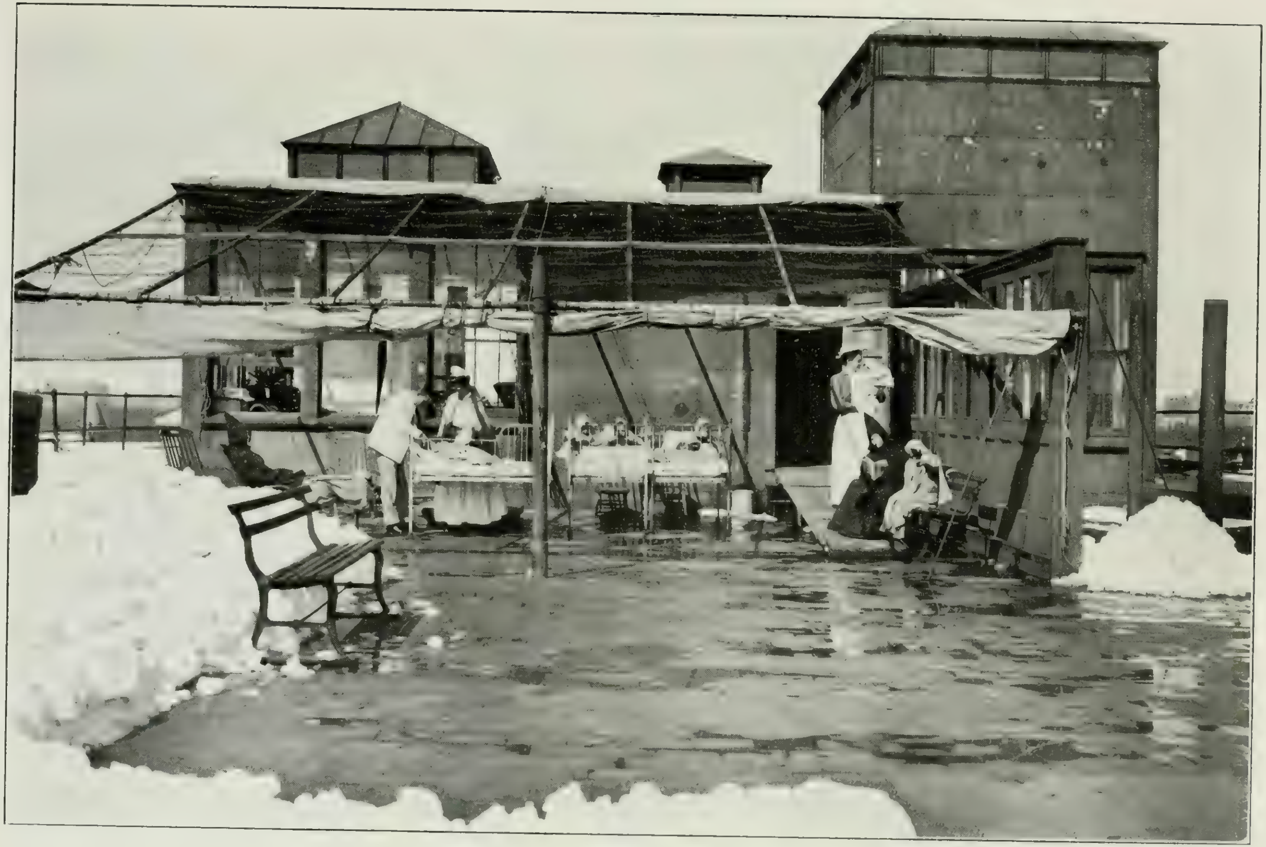


FIG. 2—"UNIMPROVED" ROOF. EAST SIDE OF SUN ROOM

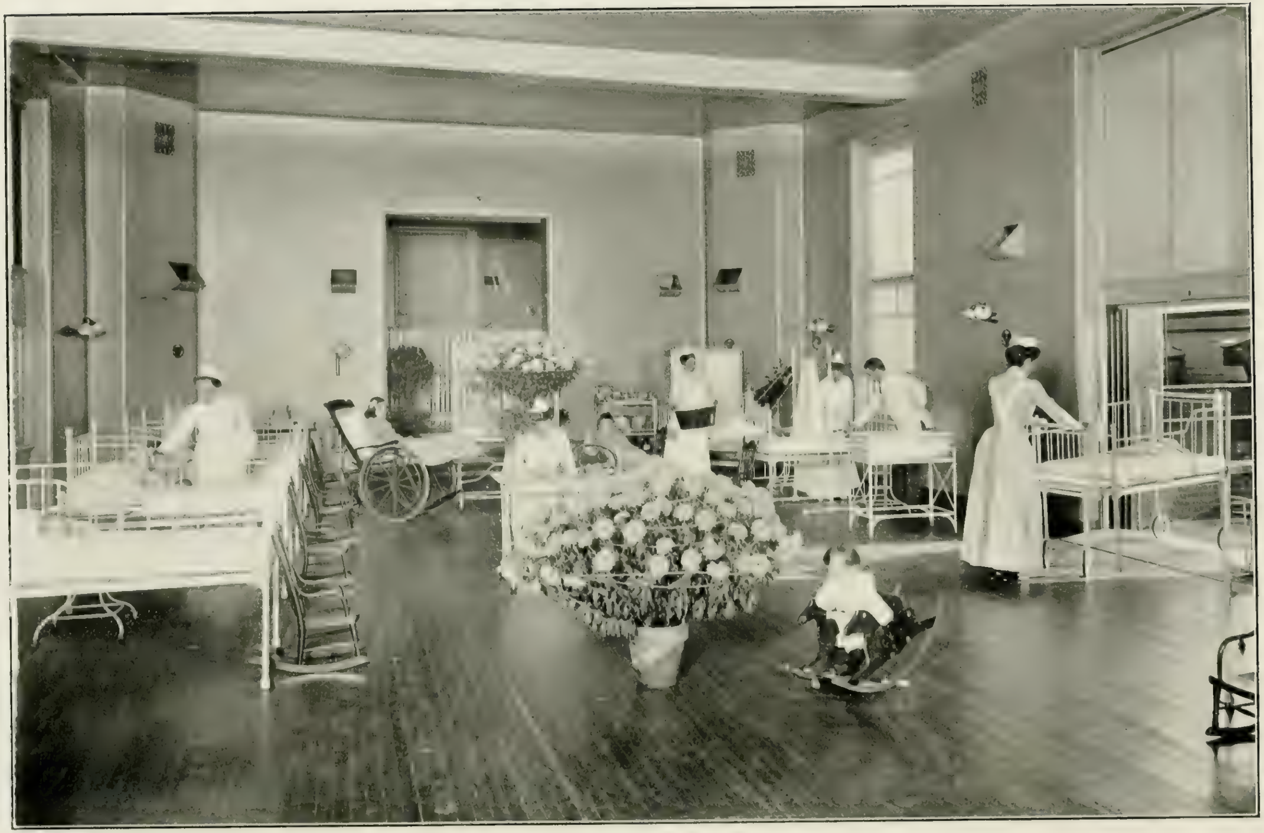


FIG. 3—CHILDREN'S WARD

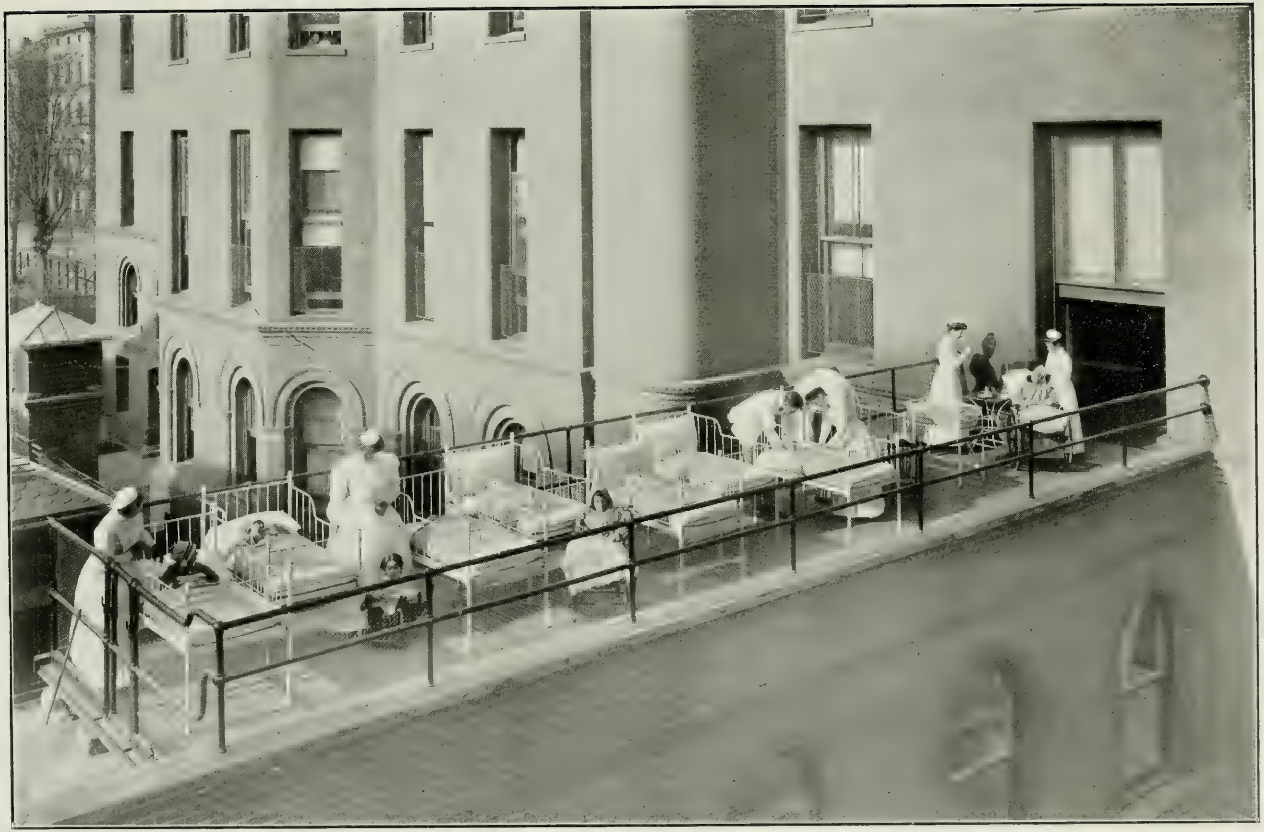


FIG. 4—BALCONY CONNECTED WITH CHILDREN'S WARD

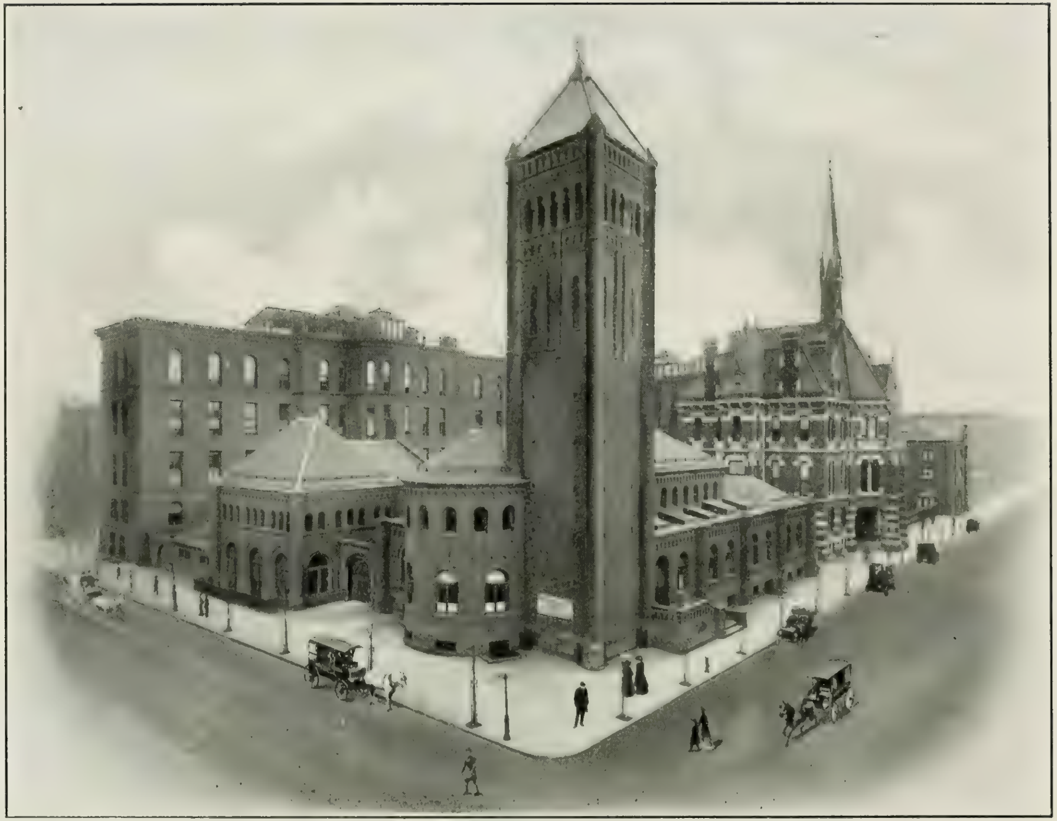


FIG. 5 ROOF-WARD ON MEDICAL PAVILION

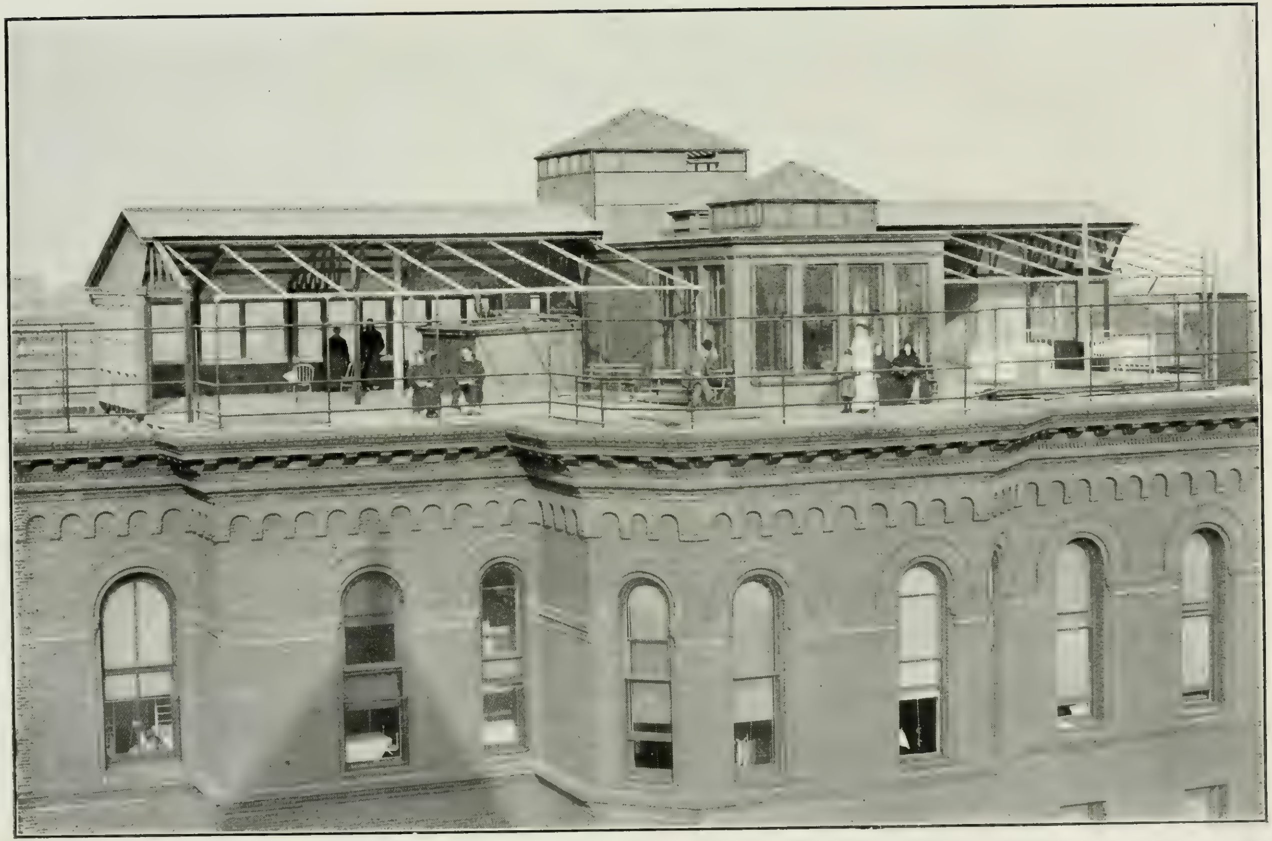
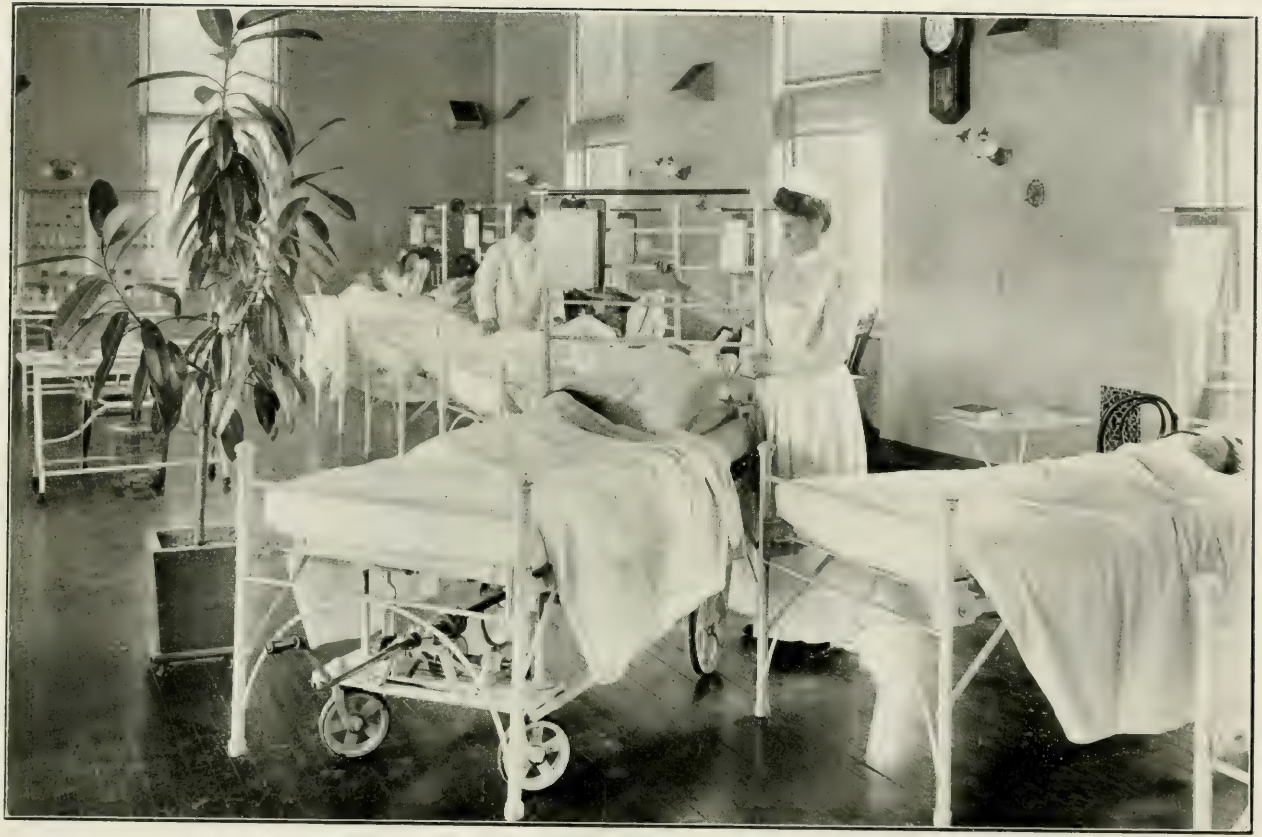


FIG. 6—STEEL SHED. SHOWING STRUCTURE JUST COMPLETED



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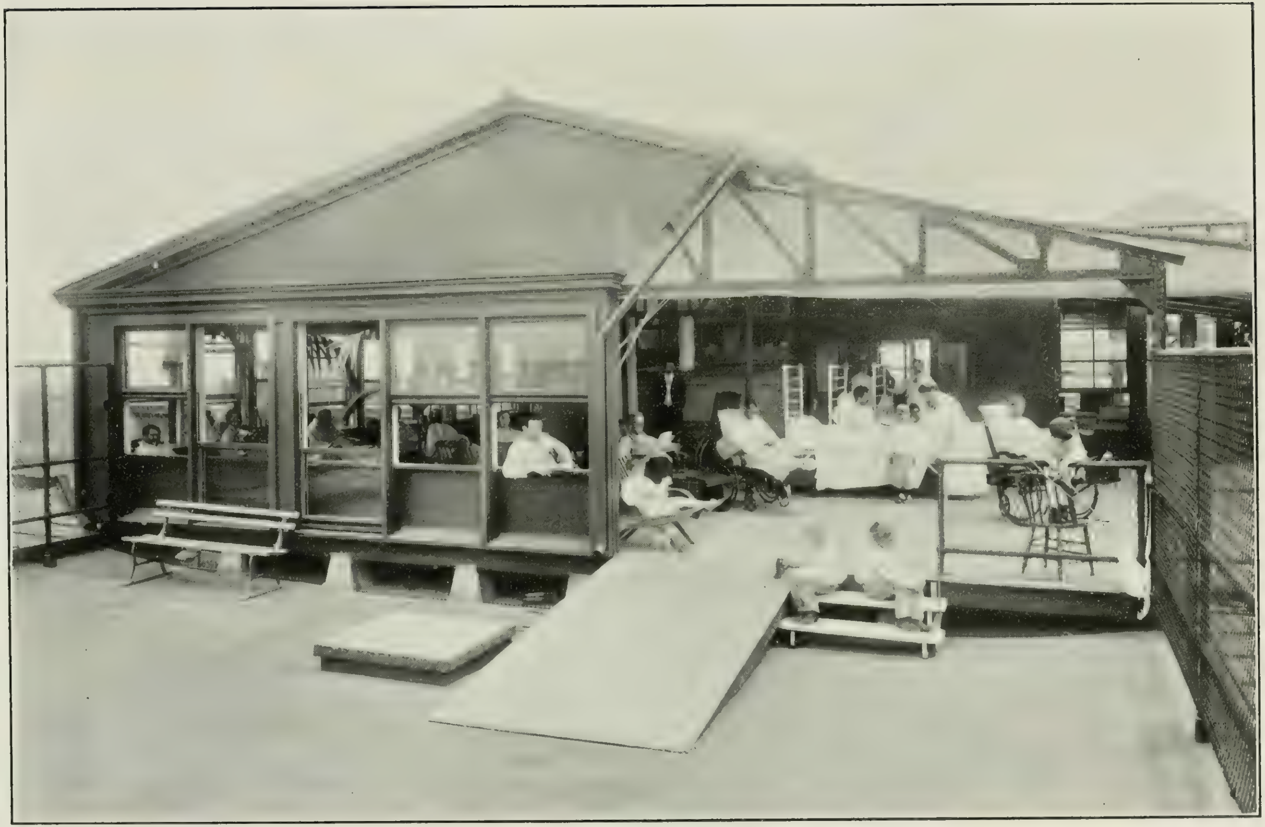


FIG. 8—OPEN AIR ROOF-WARD, WEST SIDE, COMPLETED

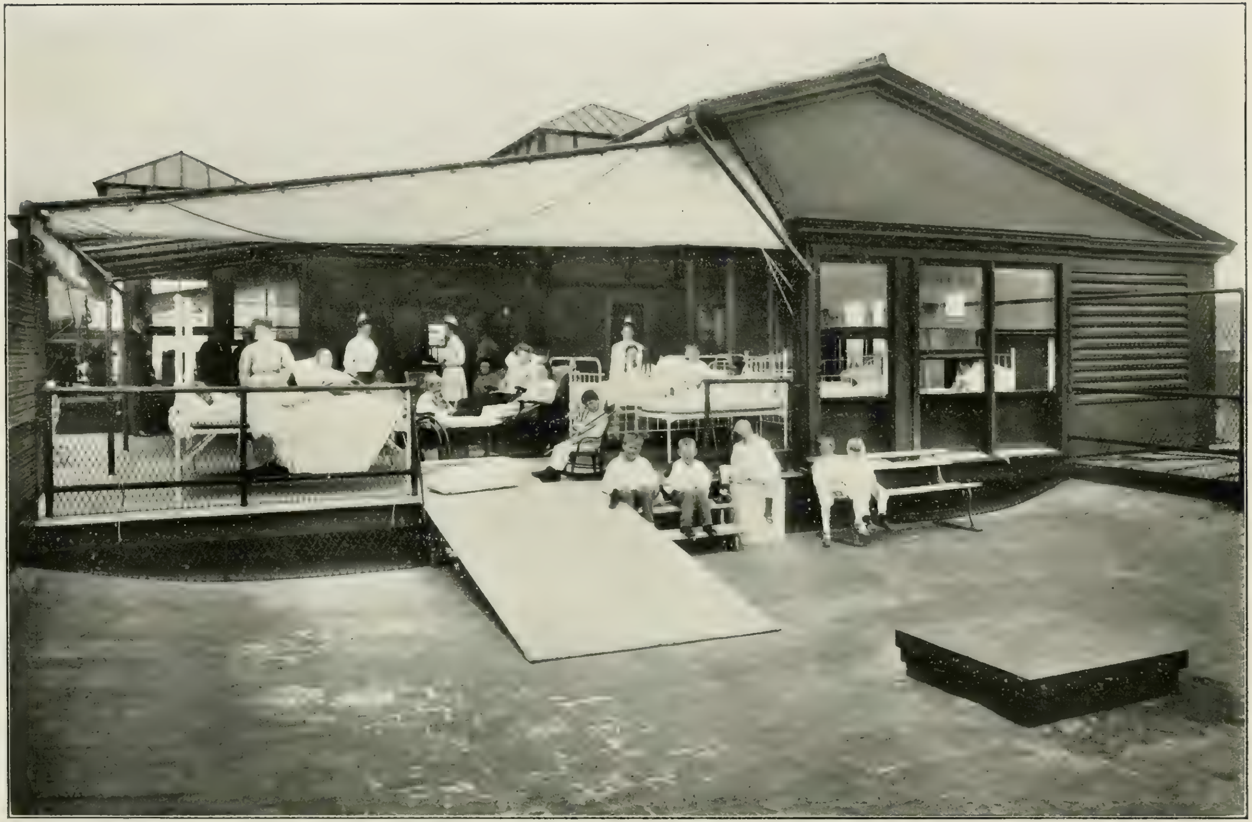


FIG. 9—OPEN AIR ROOF-WARD EAST SIDE, COMPLETED

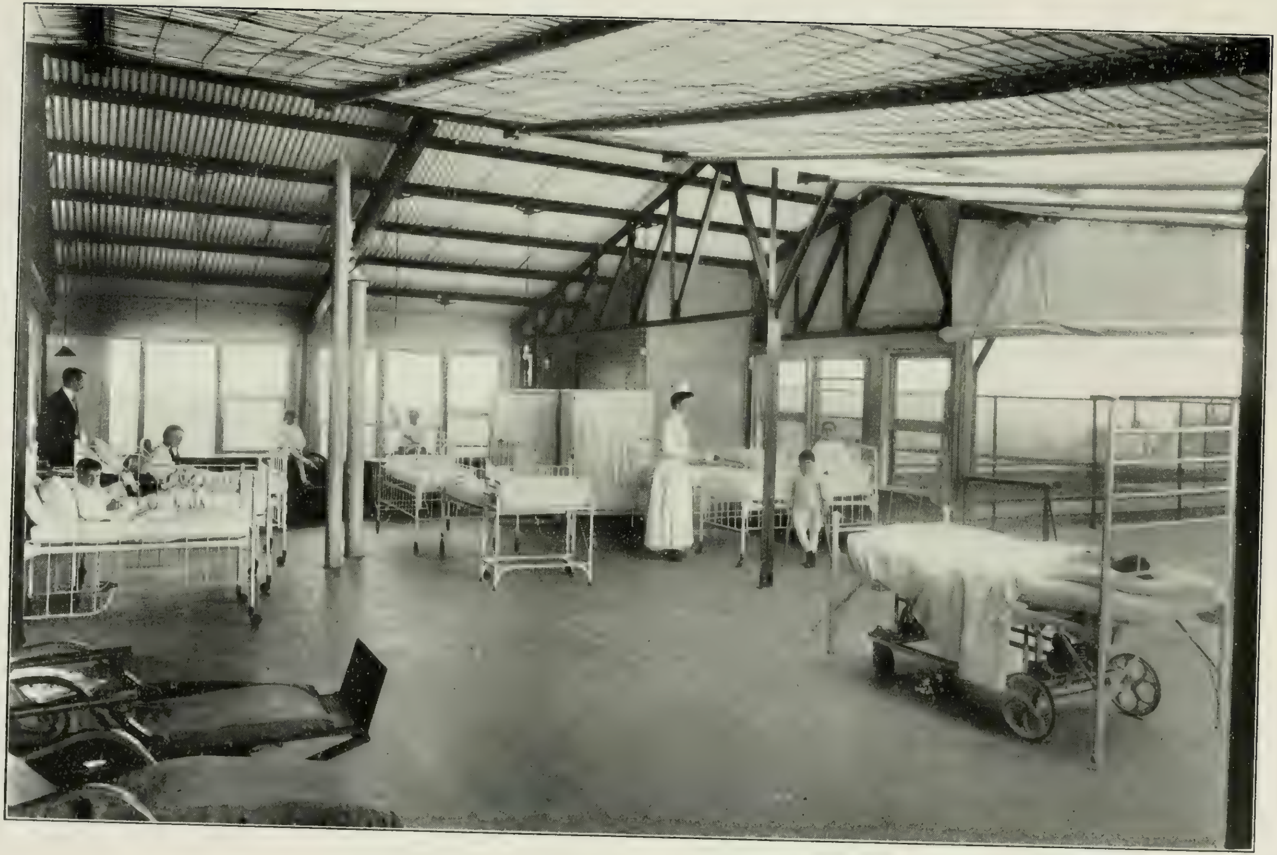


FIG. 10—EAST ROOF-WARD. AWNINGS DOWN

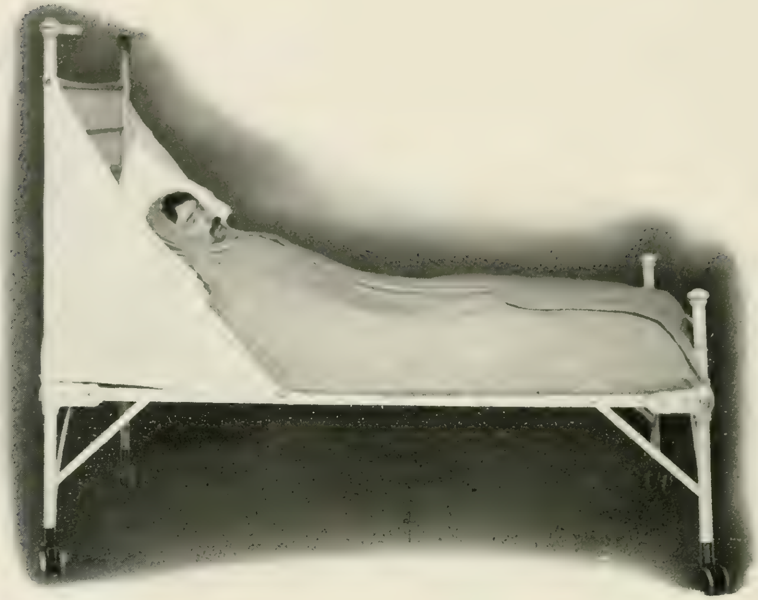


FIG. 11—APPROVED BED DRESSING FULLY ADJUSTED

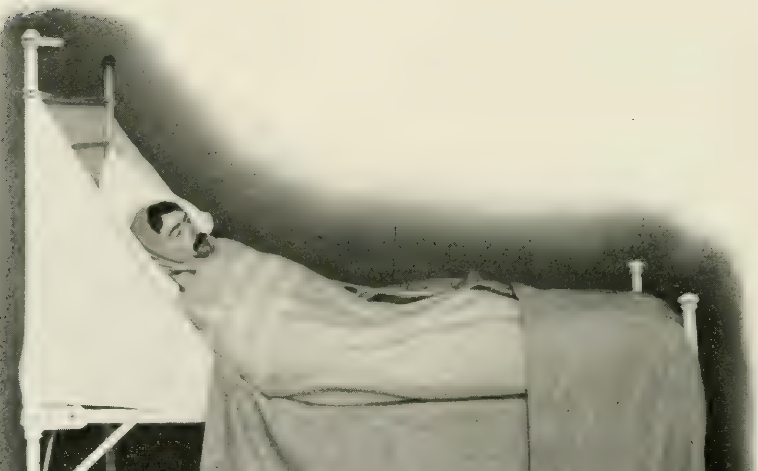
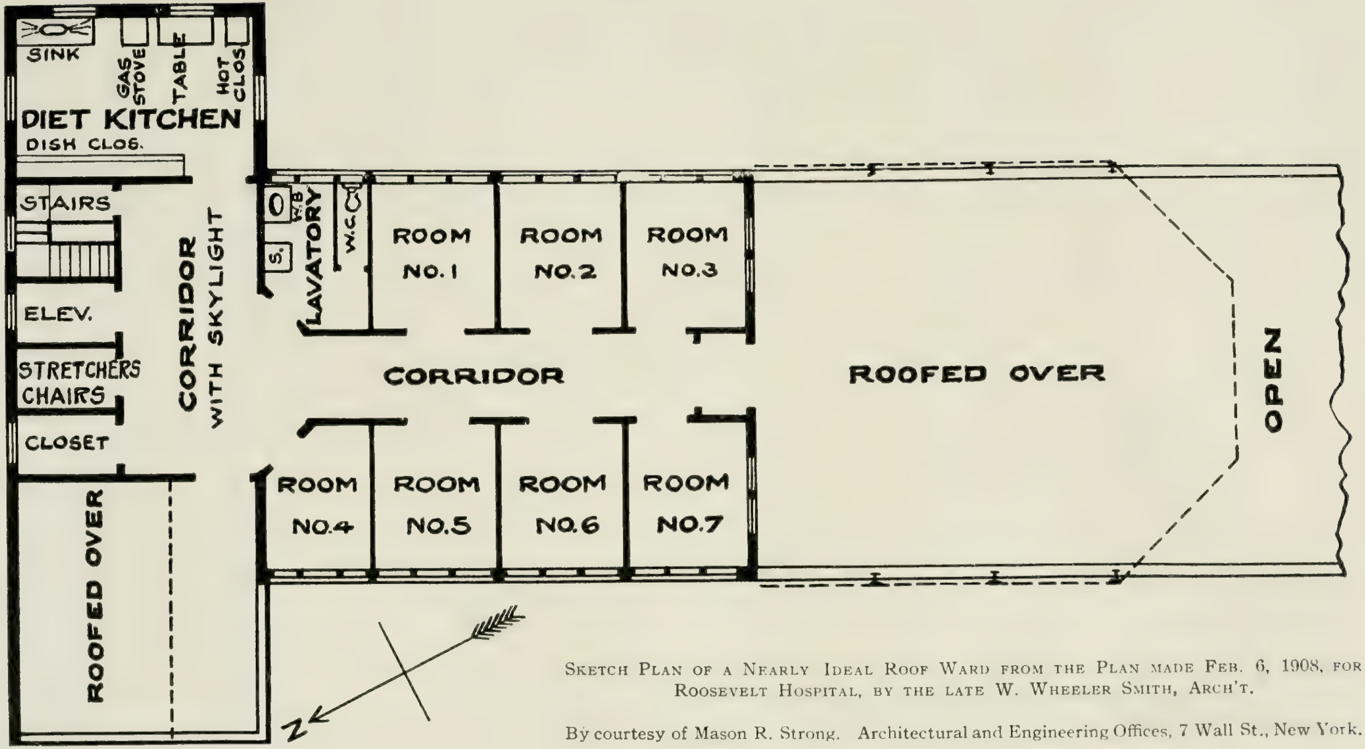


FIG. 12—ANOTHER METHOD OF BED DRESSING. PARTLY ADJUSTED.


SINK
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ROOM NO. 1
ROOM NO. 2
ROOM NO. 3
CORRIDOR
ROOM NO. 4
ROOM NO. 5
ROOM NO. 6
ROOM NO. 7
ROOFED OVER
OPEN
N

Sketch Plan of a Nearly Ideal Roof Ward from the Plan made Feb. 6, 1908, for Roosevelt Hospital, by the late W. Wheeler Smith, Arch't.

By courtesy of Mason R. Strong. Architectural and Engineering Offices, 7 Wall St., New York.

FIG. 13—NEARLY IDEAL OPEN AIR ROOF-WARD

I.

THE OPEN AIR ROOF-WARD.

By W. P. Northrup, M.D., Attending Physician.

The last Medical and Surgical Report, Vol. VII, 1906, contains a plea for the construction of an all-the-year-around open-air roof-ward on the medical pavilion. We now have it. A friend of the Hospital has financed it, the Hospital management have built it. For nearly two years this open-air ward has been in general use for children and adults, medical and surgical, acutely sick and convalescent.

So far as we know, this is the first experiment of its kind, consequently a review of the work of the ward and the general impression of its adaptability to the purposes for which it was planned, may be of value.

In May, 1905, children were first taken to the "unimproved" roof for systematic open-air treatment. The doors of the sun-room and elevator were too narrow for the passage of adult beds, so it resulted that this treatment was limited to children. Cribs on wheels, rolling stretchers, wheel-chairs and carrying in arms, were the available means of transportation. The eastern side of the sun-room, aided by a glass and wooden screen on the north side, furnished such protection that even in snow-storms of the following early winter the children were taken for six hours to the roof. This daily airing of the patients was found to be rather more beneficial than the most sanguine had expected.

The two illustrations, Fig. I and Fig. II, show a fairly representative scene on the roof before the new structure was begun.

Fig. I shows snow, wheel-stretcher, "Tommy Atkins," and east side of the sun-room.

Fig. II, a similar view, east side of the sun-room.

The two photographs show the eastern side of the sun-room and to the south a part of the ventilating tower on the corner of 70th Street and Madison Avenue. The children in evidence are convalescents from empyema and various operations. The boy standing in the foreground, "Tommy Atkins," had been operated on for empyema. His condition was poor and necrosis of the ribs followed; he was sent to the country to be built up for further operation. At the time of the photographing he was in the Hospital for the third time for the removal of the necrotic bone. His convalescence had now become so satisfactory, his flesh, color and spirit so improved, that the *personnel* of the Hospital might be pardoned for considering him a show case and a good witness to the value of systematic open-air treatment.

Within the year, 1906, the children's service was moved to a larger ward, and its capacity thereby doubled. Fig. III represents the interior of the present children's ward, ward I. The ward is well lighted and airy and is connected by a window five feet wide with an open-air platform or balcony, level with the floor of the ward. Beds and wheel-chairs are easily rolled out.

Fig. IV represents the balcony or roof-garden outside the children's ward, southern exposure. The special advantages of this roof-garden are its nearness to the ward and the fact that its entire extent is constantly under the eye of the head nurse. Nearly all the cases in the ward, those in beds and running about, can be accommodated on this balcony in favorable weather. The intense sun of summer and the severe winds of winter limit its usefulness.

On April 26, 1907, the new open-air roof-ward was open for continuous use for children. The construction of this ward, the first of its kind to be built, is thought to be of sufficient interest to those contemplating building a similar one, to justify publishing a series of illustrations of it, in various stages of building. Fig. V shows the location of the structure on the middle third of the medical pavilion, also the high railing encircling the entire pavilion's roof. Fig. V also presents a general view of the Hospital from the south-west corner of Madison Avenue and 70th Street. Fig. VI shows the steel shed flanking the sun-room, the shed facing the south and opening out upon the large platform or roof-garden. The shed is similar in shape to the horse shed commonly seen in the rear of country churches.

Fig. VII represents an adult bed, on a truck for removal to the elevator and the open-air roof-ward. Fig. VIII shows the open-air roof-ward on the west side. This scene fairly represents its common May and June use. Adult males and children are seen in beds and chairs, or moving about at will. It is commonly observed that all persons, adults and children, prefer to be upon the canvas covered wooden platform rather than upon the hard tile roof seen in the foreground. This may serve as an intimation to those planning future roof-wards.

Fig. IX shows the eastern shed and garden containing female patients and children in beds, cribs, bassinets and chairs, or moving about. The eastern side is better protected from west and north winds, and is a favorite spot in the short days of winter, and for sleeping out at night. To the extreme left of the illustration one sees the windows of the sun-room, to the right the door leading to the warm closets, and in the middle one catches a glimpse through the two doors of the sun-room into the west garden.

Fig. X gives us the eastern platform with awning drawn down as a protection against too bright sun. By means of the canvas cover and adjustable side protections, patients can be shielded from light rains and winds, and can remain out all night. One of the most interesting scenes of a great hospital is to be witnessed at midnight while the patients are sleeping. It is doubly interesting in the present instance to pass among the cribs and beds filled with sleeping children and adults, and note the quiet, profound sleep which only open-air can assure.

The following memorandum may be of use for persons contemplating building a hospital open-air roof-ward. The first roof-garden necessarily has been more or less of an experiment; others as well as ourselves may learn from its defects.

The ward:—A roof open-air ward should have all the accessories of the usual hospital ward.

Large elevators:—The cars should be large, car and door capable of admitting and carrying an adult bed with plenty of spare room on all sides.

Dumb-waiter:—There should be a separate elevator for food and supplies.

Grooming-rooms:—These are warm rooms, attention rooms, in which patients may be made comfortable in their beds before rolling them out for a long airing in the open. The grooming-rooms may serve also as breakfast and dining rooms. They should be warm, containing a basin and running water.

Diet kitchen:—This should contain steam table, gas range, sinks, drip boards, cases of shelves, refrigerator, tables, etc. The accommodations should be adequate for the preparation of soft foods for bed patients and such convalescents in chairs as are allowed to lunch on the roof. The room should be warmed.

General work-room:—This should be of liberal size, warmed, and furnished with sink.

Linen closet:—This should be fitted with shelves, and capable of being thoroughly warmed so that in winter all linen may be brought to the patient dry and thoroughly warm.

Dish closet:—This should contain shelves, the closet should be well warmed.

Toilets:—Two toilets, each containing a slop hopper, with racks for bed pans, urinals, etc. The rooms should be warmed and the racks placed just above the steam coils and thus thoroughly warmed.

Rug closets or wrap rooms:—Closets for blankets, rugs, wraps and pillows are needed and are frequently forgotten. Such storage rooms are most essential to the comfortable administration of the ward. It is safe to say these will be forgotten and seldom provided for in any similar plans.

Shed:—The shed should be of the so-called "horse-shed" type, and should face the south, its southern opening being just high enough to admit the tallest probable visitor. The shed is for use in storms and harsh winter weather. A deep shed with low southern opening is the best device. The shed should be twenty-five feet deep, North and South. The front lip of the roof, at the Southern opening, should be, approximately, six and one-half feet. Our roof ends at eleven feet from the floor. The high opening was originally designed to admit the sun to every part of the shed, while hoping to keep out the storm. In actual experience the patients seek the open in fine weather and the high roof admits storms in bad weather. To meet both we would suggest, to those planning similar roof-wards, to prolong the break in the roof down to the proper level, setting in to the same (the break in the roof), narrow glass windows in frames, capable of being turned on vertical pivots. These can be made of strong glass, admitting sun and air, also, at will, excluding storms.

Open roof garden:—This should be an open platform with a high protecting wire fence surrounding it. Maniacal patients are usually quiet in the open air and sleep, but they cannot be trusted.

The platform with wooden flooring is in our judgment the best, within reasonable cost. The hurricane deck of a steamship, with its painted canvas cover, furnishes the best type of flooring for winter roof gardens. Tiling is too cold in winter, too hot in summer, too hard and forbidding at all times. Children play up to the very edge of the present wooden platform and seldom step off on the tiling.

The open platform, the shed, the sun-room, grooming rooms, diet kitchen—all rooms should be on the same level; no door sills.

All beds, chairs, stretchers, dinner cars and lounges should be on wheels or rollers. The wheels should be of sufficient size to enable the beds or chairs to roll over all irregularities and to roll easily into the elevator. The strength of a single nurse should be sufficient to move the bed containing an adult patient anywhere on the plane of the roof garden.

For the care of children the present hospital equipment is adequate. All the beds are on wheels, and children's cribs are easily wheeled into the sun-room, which is well warmed. Fig. X shows the cribs mounted on wooden castors, also the adult bed on a "truck." The easy transportation of adults on trucks or roller-castors is a proposition still under consideration. Each bed should be so mounted on its own wheels that a single nurse can easily trundle it.

Fig. XI. Keeping bed-patients warm. This is easily done if two points are remembered. First, the patient must be clothed in practically a union suit. In extremely cold weather the patients are, in addition, wrapped in light woolen blankets, inside the sheets. Second, the mattress and the patient must be wound up in the blankets together. There should be as much clothing below the patient as above. At the Presbyterian Hospital we use ordinary bed blankets, tucking them well under the mattress and finally placing below the mattress an extra large blanket which is at last brought around over all else and pinned together up and down the middle line of the bed from the patient's chin to his feet. At the foot of the bed, the side folds meet a fold coming from beneath the feet, and the side folds and the foot fold are pinned together. There is regularly a rubber blanket beneath the patient's mattress. These last precautions make sure that no air gets in below the mattress or the upper bed clothing. Our outside enveloping blankets are specially made, of unusual size. These may be extemporized by sewing two ordinary woolen blankets together, lengthwise.

Fig. XII. The bed dressing, here pictured, seems thus far satisfactory. They are the best we have known. The patients

rest comfortably, dozing for some hours, being periodically wheeled into the grooming room to be turned, rested, fed and made comfortable. In moderate winter weather most adult patients are wheeled into the grooming room twice daily.

The arrangement of the bedding of the patient and the dressing of the nurses have required much thought and attained fair success. Bed patients must be made comfortable in a warm room and trundled out into the air for a longer or shorter time. Convalescent patients do not enjoy eating in the open air, and the so-called grooming rooms may often be requisitioned for dining purposes. Private patients' pavilions require several small rooms. These may be used as grooming or as feeding rooms as needed. It cannot be too often repeated that every facility should be provided for making patients comfortable. This is also true of the nurses. They will not favor the work and become advocates of open air treatment unless they can be made comfortable. The nurses and sitting-out patients should be dressed appropriately. They may well take a leaf from the directions of sanatoria for similar needs in dressing. The nurses serving in the open roof-wards are provided with a liberal allowance of protecting garments suitable for the severest weather. This will be the more appreciated when it is known that nurses temporarily needing themselves open air, are put upon this service. They are provided with arctic overshoes, tights, sweaters and long overcoats.

It should be thoroughly recognized that wherever cold rooms or open wards are used, in the care of the sick, corresponding warm rooms should be in intimate relation. Patients need to change positions and to rest, after long sojourns in close wraps outdoors, and nurses need a place of refuge.

Comforting texts might well be painted on three walls of the open air ward—all of them running as follows: Let every one be made comfortable.

For two years the roof-ward has been in nearly continuous service. In the very hottest weather in summer its use was discontinued for a little. It is pre-eminently for winter use. It may be safely stated that the open-air roof-ward has proved satisfactory. In some details of construction a second attempt would much improve upon the first. Open-air roof-wards and balconies are henceforth to be essential parts of hospitals and are to be considered in the original scheme of construction.

Fig. XIII. A sketch plan for a nearly ideal open air roof-ward, designed for a private patient pavilion, many or most of whose inmates are surgical. The pavilion extends North and South, the "roofed over" portions of the plan are two sheds facing the South and the "open." The narrower portion of the pavilion is thirty-four feet wide; this measurement may incidentally serve as a basis of estimate for other parts.

The sheds, marked "roofed over," are closed or capable of being closed, on three sides. The larger one has movable partitions at the extreme East and West limits of the South opening, capable of narrowing the South opening so that approximately only the middle third would be open to severely bad weather. That would leave twenty feet open to the South with corners of refuge on either sides. It will be noted that the larger shed is more than thirty feet deep.

The larger shed is for general use. The smaller shed is designed to accommodate patients recently operated on, or those, especially women, who wish for any reason to be quiet and isolated.

The rooms one to seven, opening on the corridor, are "grooming rooms," also rooms for patients desiring rest. They are not private rooms in the sense that they can be engaged ahead, but are to be disposed of according to the needs of any patients in the pavilion.

The corridors and doors are of such ample proportions that adult beds on castors can be wheeled easily in any direction.

The remaining conveniences are shown sufficiently in the sketch. Attention is especially called to the diet kitchen, its capaciousness and appointments, to the closets, store-rooms, lavatories, etc. The plan here shown (Fig. XIII) is thought by those who have acquired most experience in building and using our own roof-ward, to be nearly perfect for the pavilion for which it was designed, and the class of cases to be cared for.

Whether balconies or open roof-wards are to be preferred, we cannot finally say. The Presbyterian Hospital has both. For day and night continuous treatment, the open roof-ward has done the better service.

We are indebted to Mr. and Mrs. William K. Vanderbilt for the gift of our present open-air roof-ward.

II.

FRESH AIR TREATMENT IN HOSPITAL WARDS.*

By W. Gilman Thompson, M.D., Attending Physician

(*Reprinted from the Medical Record, February* 9, 1907.)

The general medical hospital ward, as exemplified in most of the hospitals in this city, is a most uncomfortable and irrational place for the proper care of the sick. In the same long, narrow room are crowded a miscellaneous collection of ailments, all submitted to identical conditions and surroundings, without the slightest attempt at appropriate adaptation of environment. The pneumonia patient, with a temperature of 105° F., sorely in need of fresh, cool air, lies in the next bed to the uremic patient with a subnormal temperature and high tension pulse, who needs warm air and a hot pack! The typhoid fever patient, with a racking headache and photophobia, lies facing a glare of sunlight, which is doubtless beneficial to the man with pernicious anemia in the next bed (because the trained nurses think the ward looks better with the shades all at the same height). The neurasthenic, with insomnia, lies next to the patient with alcoholic cirrhosis and delirium tremens, who keeps the entire ward awake most of the night. The convalescent patient has nowhere to go during the day for a change of air and scene, and the poor old woman with a little chronic cough, who needs to rest in an easy chair, toasting her feet at a heater, sits gazing wistfully and pathetically at a hole in the wall near the ceiling, where some architect (who never built a hospital before) has seen fit to place a hot-air register. But these are minor inconsistencies. The greatest evil of all is that the ward is "ventilated" by a thermometer, a little instrument which, from October to May, is kept steadily at 68° or 70° day and night, without regard to the moisture of the air, its freshness, its CO_2 content, its nitrogenous waste, its pollution with fetid odors, emanations from foul stools, foul breaths, and foul perspirations. Without regard, also, to the fact that during the visiting hours, or during the admission of classes of students or probationer nurses, the ward air, which ought to belong primarily to the patients, has been breathed for them by double, and sometimes treble, their number of outsiders. In some very much "up-to-date" institutions, the thermometer is replaced by an electric thermostat, communicating its valuable data to the superintendent's office, so that he may rest assured that in the wards above the air is always at 70° F., no matter if it is fifteen per cent. CO_2 or hydrogen sulphide, for all he knows. The functionary usually placed in charge of this ingenious system is the hospital engineer, who is about as much of a ventilation expert as a hibernating dormouse. The nurses (who are given elaborate lectures on hygiene, and "how to ventilate the sick-room") are not allowed to raise a window as much as a crack from October to May, and as for the house staff—why, of course it is not for mere doctors to stoop to such details! One of our representative hospitals, in which that most pernicious of all ventilating systems, known as the "closed system," was placed some eighteen years ago, with the endorsement of the Medical Board, and at extraordinary cost, originally had locks and keys attached to its windows, and in lavatories the windows were, in addition, screwed down with bolts! Would anyone of us consent to live from October to May in a house in which his bedroom windows were locked fast and his lavatory window screwed to the sill? But we are in and out, getting the stimulus of a *change* of air, a change of temperature, as well as of air composition. The bed-ridden patient, on the other hand, lies perpetually at the mercy of the superheated air which is supplied him. The fundamental fault of the "closed ventilation" system is, that heating and ventilation are made inseparable, and to deliver through long conduits air hot enough to warm a large number of distinct wards, it must be first superheated to about 400° F. and then all doors and windows must be kept tightly closed, for the opening of a single window in one ward "short circuits" the entire system, and temporarily cuts out all the wards from both heat and air supply. This system may work in large assembly halls, such as churches or theatres, but there it is not continuous, and the people come and go, and refresh themselves with normal outdoor air. Superheated air is like superheated or sterilized milk—one can live upon it, of course, but there is nothing "uplifting" about it (as Walter James has said, in writing on this topic), and it admits of no advancement in health. I am convinced that there are properties which, for lack of a better term, we call "vital" in the outdoor air, that are not measurable by any of our present instruments of precision, such as the thermometer, hygrometer, thermostat, barometer, etc. It is only a few years since it was supposed that all was known about the chemical composition of atmospheric air. Then argon and other new elements were discovered. It is not unreasonable to believe, also, that some of the physical properties of the air are more or less permanently altered by its confinement and superheating.

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* A paper read before the New York Academy of Medicine, January 17, 1907.

Being unable to find any recorded scientific data upon the quality of hospital ward air, I undertook to obtain some, a year ago, in the wards of the Presbyterian Hospital. A study of the CO_2 content of the wards was made under varying conditions. The analyses were performed for me by Dr. C. G. L. Wolf (Instructor in Chemistry and Physics in the Cornell University Medical College in New York City), and the results were very illuminating. The experiments were carefully made, unusually large quantities of air were used to lessen liability to error, and control tests were made upon the Hospital roof air and that of

Dr. Wolf's laboratory, in which the chemical analyses were conducted. Without going into details, I will quote briefly from the conclusions of our report, which was submitted to the managers of the Hospital: (1) Pure, normal, atmospheric fresh air is admitted to contain four volumes of CO_2 per ten thousand volumes of air; 4.5 parts CO_2 represent highly impure air, five parts injurious air, and six to seven parts air wholly unfit to breathe. (2) When the fresh air on the roof was practically normal (4.06 parts CO_2), that in the wards, with the most complete closed ventilation system in full operation, contained as much as 4.71 parts CO_2, and after twenty visitors and four nurses had spent one hour in the ward this content rose to 5.13 parts. Immediately thereafter the ward windows were opened for ten minutes only, and the CO_2 content fell to 4.34 parts, although on a cold December day the ward temperature was lowered thereby only 3° F. Hence, with almost imperceptible change, as shown by the pernicious thermometer, the air impurities, which had been increased more than 20 per cent. by the visitors, were nearly eradicated by ten minutes of *window opening*. Truly the nose is mightier than the thermometer as a ventilation guide! (3) Of course the CO_2 content is only one of the many forms of atmospheric vitiation, but it is known to rise and fall *pari passu* with other inpurities, and is therefore a fair index of the other conditions of vitiation. (4) In connection with these experiments, others were made by Dr. G. A. Tuttle in the bacteriological laboratory of the Hospital, to demonstrate the injurious effect of raising dust by dry sweeping, so common in American hospitals. On an exposed agar plate twenty-six colonies of bacteria were deposited in quiet ward air. When the air was agitated by dry sweeping the number rose to five hundred and thirty-two colonies, or more than twenty times as many colonies of streptococci, staphylococci, diplococci, with spores, fungi, and a variety of miscellaneous organisms. This was in a ward thoroughly cleaned every day.

Several years ago, while simultaneously visiting in two hospitals, I observed a very striking difference in certain classes of patients, especially those with marked anemias, chronic sepsis, pulmonary and chronic cardiac diseases, etc. In one the patients were supplied solely with superheated air forced through thousands of feet of metal conduits, and during their entire stay in hospital never received one single breath of unbaked air. Some of them improved, others grew well, to be sure, but they were a very long time about it. The other hospital is one of our oldest. The windows have settled, gusts of air and even the snows blow in through wide cracks. The wards are heated by steam pipes, and when too hot or too close the windows are opened, and even in midwinter are sometimes left open all day. Each patient receives good, daily allowance of pure, fresh, unroasted air. The difference was really very striking in the greater promptness of recovery in favor of the old, tumbledown hospital, that used to be an almshouse ninety odd years ago. It was so striking that we sought to do better, and as the old almhouse is the only hospital in this entire city that has adequate balcony accommodations attached to the wards, we began to move the patients' beds out on the verandas. First the tuberculous were moved out, later the pneumonias, and later still any case that could be distinctly benefited by air which had never been in anyone else's lungs. At the Presbyterian Hospital we have as yet no balconies; but we have small rooms opening off the wards. In these we have sealed up the artificial ventilation system so that the windows may be kept open day and night, and a patient at the corner of Madison Avenue and Seventy-first Street, who is dying for lack of fresh air, can get it without freezing out a surgical patient on the corner of Park avenue and Seventy-first Street, by short-circuiting his air supply! In these small rooms, as far as their capacity admits, we now place all those needing uncooked air, and the effect in certain cases is truly magical. We have made further improvement in the wards themselves by requiring that the windows be simultaneously opened widely at least twice a day, to thoroughly air the ward, like any other bedroom, and by requiring that the night temperature be kept five degrees lower than that of the day, for there is something stimulating to respiration in such change, which is lacking at the monotonous 70° F. level.

The most striking benefit of the uncooked air treatment is shown in cases of pneumonia. Delirious alcoholic patients, with profound cyanosis, when taken out of the general ward and placed at windows open day and night, become much less nervous and restless, and distinctly less cyanosed. I formerly gave such patients oxygen sedatives, whiskey, and other stimulants. In the open air they, of course, receive no oxygen, and require far less of stimulants and sedatives. During 1906 we treated in all, at the Presbyterian Hospital, one hundred and twenty-eight cases of acute lobar pneumonia. Of these patients forty-seven, or 36.7 per cent., received absolutely no drugs whatever—no stimulants, no narcotics, no inhalations, no "specifics," nothing except the occasional laxative, which anyone in bed with fever may require, and they all recovered, in the usual way, when the time came. Some defervesced by crisis, some by lysis, some in five days, some in twelve days, or other intervals. A large proportion of these patients received the uncooked air treatment and enjoyed it. The air temperature was often as low as 35° F. or 40° F. They never complained, except when some emergency required them to be taken back to the ward, as when the room was needed for some other patient in more urgent condition. They were not all thus treated, merely from lack of sufficient isolation rooms or balconies. The remaining ward patients, who recovered, received various drugs or stimulants, solely because certain complications arose which needed treatment. But I would again emphasize the fact that of one hundred and twenty-eight patients with pneumonia, 36.7 per cent. made complete recovery in the usual time, without any medication, and for the most part with their heads lying close to open windows in midwinter weather.

Other diseases that do remarkably well with open window treatment are cerebro-spinal meningitis, chronic sepsis, and all forms of anæmia. The meningitis patients become very much quieter, sleep much better, and look better in every way. A patient with a pernicious anæmia, in which the red blood corpuscles numbered only 828,000, gained over 1,000,000 red cells in a week when I took her out of the general ward and placed her in a small room with wide open windows. She left the Hospital, a few weeks later, with over 4,000,000 red cells, and a hemolobin estimation that had risen from twenty to eighty per cent.

When the pneumonia, or other febrile cases, require a cold bath or the use of a bed pan, or any procedure necessitating exposure, they are temporarily taken into the ward, or the windows of their rooms are closed, and the rooms warmed.

All this is nothing new, but it is well sometimes to preach again from old and well-established texts. Forty-two years ago there was an epidemic of typhus and typhoid fever in New York City. As the wards of Bellevue Hospital became overcrowded, five hundred and twenty patients were transferred to Blackwell's Island and placed outdoors under tents, in the late autumn and early winter. Dr. Austin Flint, in his Practice of Medicine (5th ed., p. 978), in writing of this incident, stated: "The average death-rate in the hospital wards was one in 5.97; in the tents one in 16.77." "Making the fullest allowance for the conjecture that the cases in the tents were milder than those in the hospital wards, it can hardly be doubted that the superior ventilation in the tents was the means of saving many lives." Fifty-six years ago Dr. John H. Griscom reported in this Academy the treatment, by open air, in Perth Amboy, New Jersey, of eighty-two cases of typhus fever. The patients, who were derived from an immigrant ship, had the additional advantage of being soaked by a thunder shower, and all made good recovery from the fever. (Flint, *loc. cit.*). Eighteen years ago, during a reconstruction of the Presbyterian Hospital, after the fire, I treated a number of cases of erysipelas, with high fever, in open tents on the Hospital grounds, with excellent results. Every midwinter army campaign in which the sick and wounded have had tent treatment has shown anew the advantages of outdoor air. In answer to those who object to giving a pneumonia patient first-hand, unbreathed, uncooked air (and such objectors have usually never seen the treatment tried), it should be stated that this form of treatment is not a temporary fad or a "fresh-air crusade," but a very old, well tried, and widely tried, common-sense method, from which we have been somewhat led away of recent years. The undesirable necessity of building large metropolitan hospitals of the "sky-scraper" type, the idea of massing all manner of heterogeneous cases, with a series of long wards, all precisely the same, like sheep corrals, and the inhumanity of architects, who strangely prefer mansard roofs and straight ornamental facades to roof gardens and ward balconies, pernicious application of wholesale ventilation "systems" for the air supply of the air-hungered—these are some of the factors which have led us to turn from the open window and fix our exalted gaze upon the cast iron heater in the wall!

In Continental Europe they are far ahead of us in modern hospital construction in many different countries. Closed ventilation systems are practically unknown. Windows are built with transoms of different sizes, permitting easy regulation of the ward air. Heaters, porcelain stoves, and even open fires, are placed where patients who feel cold and need warmth, may sit and be comforted. Numerous small rooms of variable sizes, admit of the scientific classification of patients, especially as regards their individual requirements for ventilation and air temperature (two essentially different things). Attractive day rooms are provided next the wards, so that convalescents not only obtain change of air, scene, and occupation, but leave fresher air in the wards for the benefit of the very ill. Many visitors are thus kept out of the wards by being admitted to the day rooms instead. The evil of dry sweeping in the wards is unheard of. Finally, broad, open corridors abound, and attractive grounds, with shelter tents, are so arranged that patients have free access to them at all times. In all these things we have very much to learn, especially just now, while propositions are already before us to spend $29,000,000 (see Medical Record, January 5, 1907, Stephen Smith on "A Hospital System for New York") of the taxpayers' money for new public hospitals.

I have purposely, thus far, omitted mention of tuberculosis, because the object of this meeting is to stimulate interest in the application of fresh air--not necessarily cold air, but always fresh air--treatment to a very large variety of other diseases. Tuberculosis has demonstrated for us that fresh air acts not as a specific for any one disease, but by increasing the resisting power of the organism, against many diseases. To this end we should learn to adapt our modern hospital construction as well as that of our own homes.

The following conclusions for the betterment of ward ventilation in this cold and very changeable climate are submitted:

1. Ward heating and ward ventilation should be capable of independent adjustment at all times.

2. The night temperature of the ward should be at least 5° F. below the noon day temperature, which latter should not be above 68° F. or 70° F.

3. The ward windows should be furnished with transoms and one or two movable separate panes, to admit of easy regulation and ventilation.

4. No window should be so heavy that it cannot be readily handled by the nurse.

5. The ward should be in communication with balconies or porches, on to which patients' beds may be moved through windows of the casement type. Such balconies need not interfere with the adequate lighting and ventilating of the ward, as proved at the Bellevue and other hospitals in which they have been used. (They are being put upon all the wards of the new Bellevue.)

6. The building of very large wards should be discouraged and a greater number of small adjacent rooms should be provided to admit of the scientific adjustment of the ventilation and temperature to suit the requirements of different patients.

7. The windows of the ward, even on the coldest day, should be opened at least twice daily, in the early morning and late afternoon, for a few minutes, to thoroughly change all the air in the room. During this time any patient may be covered temporarily with extra bed clothing if there be fear of exposure from draft. The same procedure should be carried out immediately after visiting hours.

8. Day rooms should be provided for convalescents where they can obtain change of air and scene, and leave more fresh air for the bedridden patients in the wards.

9. The ward should have at least one accessible heater, where patients temporarily sitting up may gather and warm their feet if desirable.

10. It is entirely unnecessary to have all the ward windows precisely alike, except from some fanciful esthetic standpoint. Thus certain windows of the casement type should spring from the floor and give onto balconies. Obviously heaters cannot stand in front of these windows, as they should in front of other shorter windows of the ordinary height. Windows should be grouped with more reference to sunlight exposure, ordinary wind exposure, etc., than is usually done.

11. House staff and nurses should not only be taught ventilation theoretically, but made to put it into practice in the wards, and should be made to regard fresh air as of equal importance with fresh food.

Where these simple common-sense principles are in daily practice it is possible to use fresh air as a definite therapeutic means and secure most gratifying results. Finally, air temperature and ventilation are *not* synonymous terms!

III.

THE TREATMENT OF PNEUMONIA, ESPECIALLY BY OUTDOOR AIR.

By W. Gilman Thompson, M.D., Attending Physician.

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In 1906 there were treated in the Presbyterian Hospital in New York one hundred and twenty-eight cases of acute lobar pneumonia. The patients were of every age and the cases were of every sort, many of them alcoholic, and many constituting the terminal factor in chronic diseases of necessarily fatal type. An interesting fact is that among others who recovered were forty-seven patients (or 36.7 per cent. of all the cases) who received absolutely no medicinal treatment whatever, except the occasional laxative which any bedridden febrile patient may require. No cardiac stimulants were given, no hypnotics, no vaso-dilators, no inhalations, no empirical remedies. These patients were for the most part treated with good fresh outdoor air throughout their entire illness. They were placed either upon a roof or in small rooms where the artificial ventilators were sealed up and the heads of their beds set at the windows, kept wide open day and night, often with the thermometer below 35° or 40° F. I commend such facts to those who are addicted to writing articles for medical journals entitled "Ten cases of lobar pneumonia with nine recoveries, all treated by large doses of quinine," or nitroglycerin, or digitalis, or cold compresses, or guaiacol carbonate inhalations, or what not. I, too, have faithfully tried all these and many other "systems" of treatment in this disease, year by year, with the growing conviction that the only rational treatment of lobar pneumonia is the symptomatic one. Not all patients need digitalis, because not all have weak hearts; not all need aconite or nitroglycerin, because not all have initial high tension and full arteries; not all need poultices or ice-bags, or cold compresses, because not all have local pain. It is well enough and time enough to employ such remedies in any special case when the need arises, but never with the idea that the natural progress of the disease can be uniformly modified, much less aborted by them. But what every pneumonia patient does require is a plentiful supply of flowing fresh outdoor air, which has never been in the lungs of anyone else, as ward air and room air always has been, and which has not been heated or roasted until it has lost all power of invigoration. In order to deliver furnace heat in a room, or air hot enough to warm a large ward, such air must previously have been cooked over hot pipes or steam coils, often to a temperature of 300° or 400° F., so rapidly does it lose heat in its conduction through long ducts and by mixing with the air of the room. In the Presbyterian Hospital, for example, I found that all the ward air in winter supplied by the "closed ventilation" system was previously roasted in the basement to 400° F. One would not feed a patient with scurvy upon sterilized milk, nor a patient with anemia upon canned vegetables, and why feed a patient with the extreme air-hunger of pneumonia upon baked air?

Moreover, it was found by analysis, made for me by C. G. L. Wolf, that in those same wards, after twenty visitors had been admitted for an hour with four nurses and two doctors, the carbonic acid content rose to 5.13 parts per ten thousand as compared with the normal 4.06 parts in the fresh air outside, an increase of twenty per cent. In any private room in winter with a very ill pneumonia patient there are also usually two nurses, one or more of the family, and the physician, all of whom, by frequent visits, share in breathing the air which has been already superheated. One finds such rooms in which, with windows tight shut, canned oxygen is being constantly liberated, after it has been superheated and confined for some time in a metal receptacle and finally blown through stale water and an unpleasant rubber tube. I formerly advocated its employment myself, but it is so much cheaper, simpler, and better, to open the window! In round figures the normal atmospheric air contains twenty per cent. of oxygen, of which only five per cent. is removed by the red blood cells in respiration, which are practically saturated with oxygen under normal conditions of atmospheric pressure. The remaining fifteen per cent. of atmospheric oxygen is returned unused in the exhaled air. Canned oxygen differs from air in that the eighty per cent. of nitrogen of the air has been replaced by oxygen. But if there is already a margin of fifteen per cent. of oxygen in fresh air, or three times the actual need of the organism, what is the object of adding more? The normal saturation of the red blood corpuscles prevents their carrying any more oxygen, nor can the plasma absorb it under conditions of normal atmospheric pressure. What canned oxygen may do is to replace some of the vitiated air that over-zealous friends or nurses pollute about the patient's bed. Hence it may be worth five dollars a can when they cannot be kept at a distance and will not allow the window to be opened for fear of a "draught." But the patient's chances of life are all on the side of fresh air. If he be entirely outdoors, on a balcony or roof, there is no "draught." If he be at an open window there is less danger of a draught the wider it be open, that is, of a chilling current of rapidly moving air. If he be wrapped up, as he should be in cold weather, precisely like a tuberculous patient, with extra blankets, a hot water bottle to the feet, and a woolen hood closely enveloping his head, no draught will ever harm him.

In such treatment of pneumonia I have learned to discard the "draught" as a bogie born of prejudice and inexperience. When the bowels are to move or when hyperpyrexia requires a cold pack, which latter seldom occurs with patients treated outdoors, they are temporarily moved into the ward.

In the wards of Bellevue Hospital is found what is probably the largest alcoholic pneumonia service in the country, because the service is given to the sick poor, not a few of them being the lowest type of diseased, underfed and more or less chronically drunken emigrants. The buildings are ninety years old (although new ones with verandas opening off every ward are in process of construction). The main buildings are faced with balconies intended originally for fire escapes, but large enough to accommodate a number of ward beds. For the past few seasons it has been my constant practice to treat all pneumonia patients, as far as practicable, by moving their beds out on to the balconies through the ward windows, which are cut down to the floor. The results have been most gratifying. It is the universal testimony of the nurses that they have much less "nursing" to do, the patients are so much quieter, less actively delirious, or less complaining, and they sleep so much better. It is the universal testimony of the patients themselves, as their mental state improves, that they feel better outdoors. When they are necessarily returned to the ward for special reasons, or because the service is so overcrowded that they must give place to the more seriously ill, they often beg to be returned to the outdoor air. When we cannot place them on the balconies we place the beds by open windows and keep off the ward air, as far as possible, with screens. The balcony floors are of wooden slats, and sometimes, last winter, we had to place rubber sheets over the beds to protect them from the drip of melting snow above. Sometimes it was so cold that the sputum froze in the cups.

In not a single instance, in either of the hospitals to which I have referred, have I had cause to regret the open air treatment, or known any difficulty to arise from it. At Bellevue Hospital I hesitated at first for fear some delirious patient might leap off the fire escape, as they often attempt to leave their beds in the wards, and there is an insufficient number of nurses to watch them at every moment. I therefore had protective wire nettings put up (heavy tennis netting). The nurses and house staff soon learned, however, that the patients who were actively delirious in the wards, became so much quieter after a short interval in the open air, without hypnotics, that we now seldom hesitate to leave them temporarily by themselves. They are also less restless, less cyanosed, and sleep much better.

It is not claimed that the open-air treatment of pneumonia is always curative by any means, but it often is, and the advantages above enumerated are not only very great, but are uniformly obtainable. In alcoholic subjects, especially, it is found that much less stimulation is required, and it is often possible to do without it altogether. Formerly I gave large quantities of alcohol in cases of pneumonia in alcoholic subjects, anticipating delirium tremens, but now I rarely find it necessary to employ it at all. Neither is it claimed that every patient having pneumonia should be placed at once in the open air, no matter what the weather may be. As in every other form of treatment there are cases in which routine is undesirable, such as may arise among the very aged or very feeble marasmic infants, or patients having serious cardiac disease, in other words, asthenic cases with low temperature reactions. But even among this type benefit is often obtained and the principle is the same, although modifications as to air temperature or other precautions may be desirable. It is not necessary that the air temperature should be cold, but fresh, that is, *uncooked* it should be always. Moreover, the natural changes in air temperature and moisture, as between night and day atmosphere, possess undoubted physiological value for those in health, which is missed in a monotonous climate. How much more are they missed by the cyanosed, dyspnœic patient compelled to breathe cooked air at the same temperature day and night. Many a chapter upon the hygiene of the sick-room begins with the fallacious postulate, "The air of the room should be kept uniform at 68° or 70° F.;" that is, the air may be ever so "stuffy," the nurse may have breathed it before the patient, it may have no vitality whatever, but if the thermometer declares it to be of the correct temperature, it goes! How much more reliable a guide is the educated and appreciative nose than the thermometer.

It is no new principle which is enunciated herein. From time to time for many years the open-air treatment has been advocated for pneumonia as well as for many other diseases, but it becomes desirable at times to restate old principles in the light of new experiences, and I submit that the physician, not the architect, is the proper person to treat pneumonia. The architect arranges elaborate "closed ventilation" artifical systems, automatic thermostats, and all manner of appliances and structural devices in hospitals and houses for the maintenance of uniform temperature. The physician disregards routine, opens the windows, vivifies the air, permits the patient to have the same advantage of natural air changes when he is ill that he may have when he is up and about, and even rescues him from the architect altogether by placing him sometimes outside the house. As Walter B. James has said, in writing of this subject, "The time is soon coming when the hospital roof will be defined simply as 'the floor of the top story.' "

In order not to be misinterpreted as an advocate of a "fresh-air crusade" I would add that when patients with pneumonia have very weak hearts they should have digitalis, irrespective of theoretical considerations as to intrapulmonary blood pressure; when harassed by cough they should have codeine (heroin being too depressing); when distressed by pleuritic pain they should have codeine and a poultice too, if they wish it, or an ice-bag if that gives more relief, for neither makes the slightest modification in the natural progress of the disease, because neither heat nor cold, superficially applied, reaches the deep-seated area of inflammation.* When the patients have insomnia they should have trional, as being a non-depressant hypnotic. If they have alcoholic delirium, they are best controlled by paraldehyde, or, in grave emergency, hyoscine, but morphine is to be avoided if possible, as small doses occasionally produce overwhelming results in pneumonia. For hyperpyrexia (104.5° F. +) they should be given cold sponge baths, and for sustained very high temperature, cold packs. For pulmonary œdema they should be cupped and given atropine hypodermically. Tympanites should be avoided as a very menacing symptom, because not only is the natural freedom of the diaphragm restricted and breathing seriously interfered with, but intestinal autointoxication is added to the pneumonic toxemia. Hence the desirability of using purgatives, enemas, intestinal antifermentatives such as salol, and turpentine stupes, whenever this most serious complication threatens. It is well also, temporarily, to remove milk from the dietary, as in typhoid fever with tympanites. Abundant water should be drunk to promote elimination, and the ordinary diet should consist of soups, broths, beef juice, eggs, farinaceous gruels, and milk. Oranges and weak coffee may be taken.

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* See the writer on "Local Thermotherapy," New York Medical Record, April 13, 1907.

With this simple but effective armamentarium one may deal satisfactorily with the greater number of the more serious cases of pneumonia, but it will be found that much of it, simple as it is, may be unnecessary if the patient has continuous access to fresh free flowing air.

IV.

ON THE DIFFERENTIATION OF COMMON TYPES OF PROTRACTED FEVER.

By David Bovaird, Jr., M.D., Associate Visiting Physician.

The anxiety aroused by the presence in a patient of a continued fever for which we can find no adequate cause is well known. Of recent years a number of interesting and instructive cases of this character have come under observation in the Hospital and a review of them may prove of value. We may classify these cases under the following heads:

1. Typhoid.
2. Tuberculosis.
3. Septicemia.
4. Influenza.
5. Unexplained Fever.

The absence of malaria from this list may be thought remarkable, but it is now established beyond question, that in this latitude malaria can easily be recognized by the examination of the blood and the use of quinine. A fever which shows no parasites in the blood and does not yield to quinine is not malaria. We have therefore no longer any difficulty from that source.

I. Typhoid Fever.

Protracted cases of typhoid fever are not uncommon. McCrea gives the average duration of the primary attack as twenty-nine days, but it may well be prolonged to forty or fifty days. We have in our records one case of sixty days, and longer cases are reported. Such prolongation of the fever always gives rise to anxiety, although, as a rule, if the fever is the chief consideration we may be confident of a favorable outcome. The greatest cause of anxiety in these cases is usually the diagnosis. As the fever is protracted beyond its usual limits we begin to question whether the diagnosis is certain, whether we may not be dealing with some other disease, *e. g.*, tuberculosis or septicemia. In the days when we were forced to rely wholly upon bedside observation this uncertainty often gave rise to great concern. The aids brought to our assistance by the clinical laboratory have lessened our difficulties. By means of the Diazo reaction, the leucocyte count, the Widal reaction, and finally blood cultures, the diagnosis of typhoid can now be established with such certainty that there is rarely ground for doubt. We sometimes fall into error by persisting in regarding a case as typhoid despite the negative evidence of these various tests. If in any case believed to be typhoid we have not by the end of the third week obtained satisfactory evidence, from clinical observations and laboratory tests, of the correctness of that diagnosis, we had best seriously review it.

The question naturally arises, what is satisfactory evidence of typhoid fever in the cases of protracted fever of which we are speaking? The enlargement of the spleen so often made much of belongs also to the very diseases with which typhoid is most likely to be confused, tuberculosis and septicemia. It is perhaps more frequent in typhoid than in either of the other fevers, but not sufficiently so to render its presence of definite value. We may say the same of the abdominal symptoms, distension, tympanites, diarrhœa. In short, on the clinical side the symptom of most help is the typhoid roseola. In the Johns Hopkins study of typhoid, the eruption was found in 93% of the white patients, in 55% of the black. Taken in conjunction with other symptoms suggestive of typhoid it may be safely accepted as determining the diagnosis. The characteristic rash consists of small round, discrete, rose-colored spots, varying from 2–4 mm. in diameter, disappearing on pressure, either flat or sufficiently raised to be definitely felt above the surface, developing in successive crops on abdomen, chest, or back. These spots usually appear during the second week, but it is to be remembered that they may not appear until much later—in some cases not until the fever has subsided. The bright color of the spots seen on their appearance fades gradually in three to five days, leaving possibly a slight brownish pigmentation. The typhoid spots never become vesicles or pustules and are never acuminate. They are therefore easily distinguished, as a rule, from chance eruptions of acne, miliaria, and the like. No such spots are seen in the other fevers here under consideration. The only prolonged fever in which spots not easily distinguished from those of typhoid do occur is trichinosis, but this affection is readily recognized by other features, especially the edema of the face, pains, leucocytosis and eosinophilia.

Of the laboratory tests the Diazo reaction is of slight value. It is more frequent in typhoid than in other fevers, but not sufficiently so to render its presence more than suggestive.

A persistently low leucocyte count with or without a relative lymphocytosis belongs either to typhoid or tuberculosis.

The Widal reaction, if obtained repeatedly by a qualified observer, ought to be pathognomonic. Its continued presence in a doubtful case is regularly decisive. While we know that the reaction may be absent in some cases, we also know that it is found at some period of the fever in 95% of the cases in which it is carefully sought. Its value in the case of doubtful protracted fever is therefore great.

The demonstration of typhoid bacilli in the blood is, of course, conclusive. Equal importance attaches to the demonstration of the bacilli in the urine, or cerebro-spinal fluid, or even in the feces. The cultivation of the bacilli from any of these sources is, however, attended with considerable practical difficulty. Where one has access to a first-class laboratory and an experienced bacteriologist these procedures may clear up a case which would otherwise remain a puzzle.

The following case well illustrates the difficulties of diagnosis even when every resource at our command is employed, and the value of the Widal reaction and blood cultures, when positive results are obtained.

M. B., aged forty-six years. Housewife. She had had a chronic endocarditis for some years, and was treated in the Presbyterian Hospital from April 3rd to May 12th, 1907, for Lobar Pneumonia and Chronic Endocarditis. She was readmitted on September 27th on account of an increase in her symptoms of cardiac failure. Under treatment her condition improved. The temperature was practically normal until October 20th, when she had a chill and a sudden rise to 104°. At this time the pulse, previously ranging from 60 to 80, rose to 96–108, and her dyspnœa was somewhat increased. Nothing in the physical examination at this time explained the chill and fever. For two days following the chill the temperature was moderately high, 101°–103°. then it rose again and remained from 102°–105° for many weeks. The pulse remained rather slow in proportion to the fever. The spleen became enlarged so that it was easily palpable. The abdomen was distended and tympanitic. The bowels were constipated. At times the patient's mind was rather dull, but not remarkably so. She sweated profusely. The diagnosis lay between typhoid fever (acquired in the ward) and an added infection of the endocardium (malignant endocarditis). For five weeks there was no material change in the conditions. During this period the urine regularly gave the Diazo reaction of Ehrlich; the leucocytes ranged from 10,000 to 12,000, but on one occasion sank to 6,000. Repeated trials of the Widal reaction resulted negatively and two blood cultures gave no growth. Neither the characteristic roseola of typhoid nor the petechial rash of malignant endocarditis appeared. On the whole the clinical course seemed to favor the diagnosis of typhoid fever, but the rarity of typhoid infections in the Hospital and the absence of conclusive evidences of typhoid kept us in doubt. On the other hand the suddenness of the onset and a certain intensification of the signs of the chronic endocarditis strongly suggested the possibility of malignant endocarditis, and none of the findings were conclusively against that diagnosis. On the 37th day of the fever the Widal reaction was obtained, and this finding was confirmed three days later, while a blood culture taken on the 36th day gave a growth of the typhoid bacillus. The patient finally succumbed in the ninth week of the fever and the autopsy confirmed the diagnosis thus tardily established.

The further consideration of the differential diagnosis will be taken up in connection with the discussion of the types of protracted fever.

II. TUBERCULOSIS.

The tuberculosis which belongs to our subject is the acute miliary form, of which there are two fairly distinct types.

1. The typhoid. 2. The pulmonary. A summary of two cases illustrating these types follows:

H. G., aged 27. Admitted June 23rd, 1904. Died August 3rd, 1904.

History: Family: Negative. Personal: Negative. Previous: Pleurisy—5 years ago for one week. Gonorrhea—1½ years ago. Present: For two weeks easily tired and lacking in energy. 9 days in bed on account of headache, backache and fever. He has felt better, but remained in bed on orders. On admission T. 104°, P. 72, R. 20. Physical examination at this time entirely negative

Course:—Continued fever, from normal to 105°, 8 weeks in all. Usually from 100°–102°–103°. Pulse from 72–100, more rapid and feeble at end. Respiration 20–28. Loss of flesh and strength, and exhaustion, moderate anemia.

Physical Signs: Spleen became palpable. No distension or tenderness of abdomen. No eruption. Signs of a slight general bronchitis. Laboratory Tests: No Widal—no Diazo—blood cultures negative.

Cultures from feces—no typhoid bacilli.

Sputum always negative—rarely obtained.

Urine: 40 to 50 ounces.

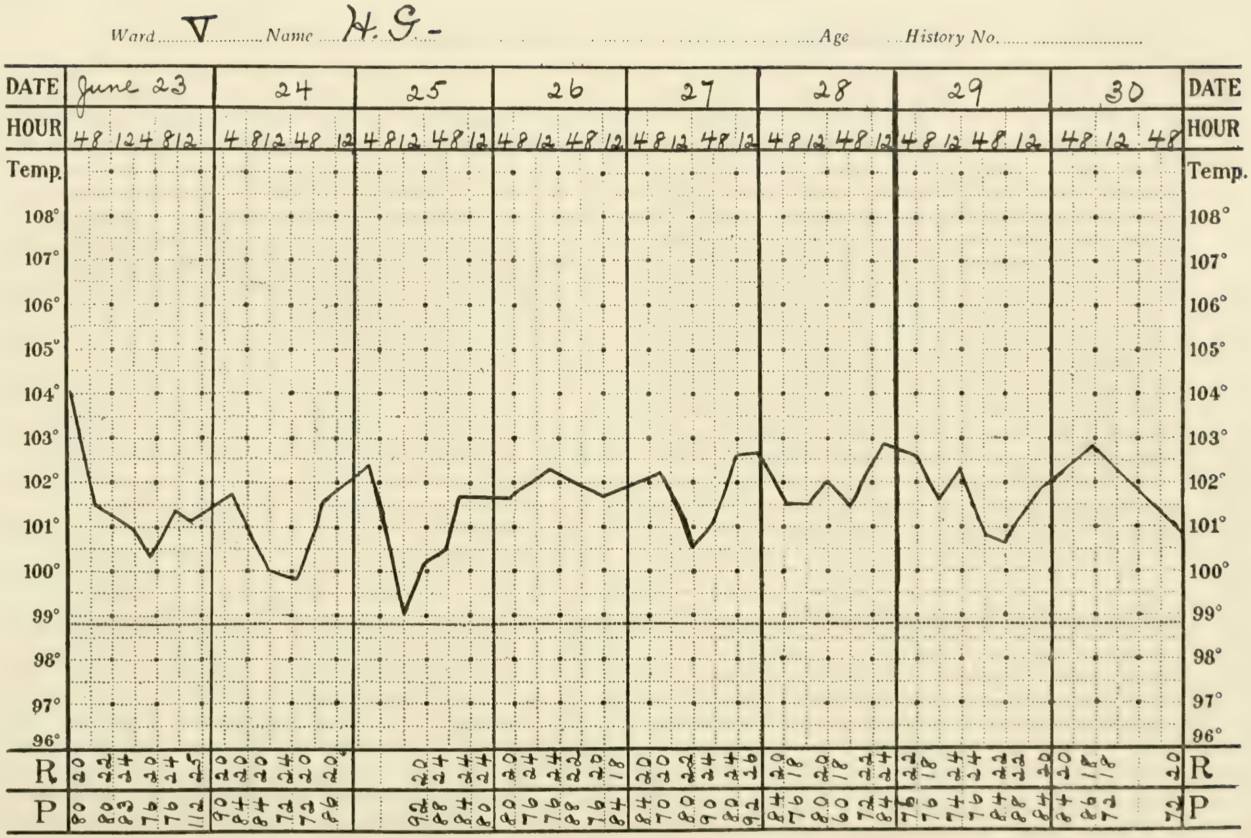
1010–1020 Albumen, a faint trace—no casts, pus or blood.

BLOOD EXAMINATIONS.

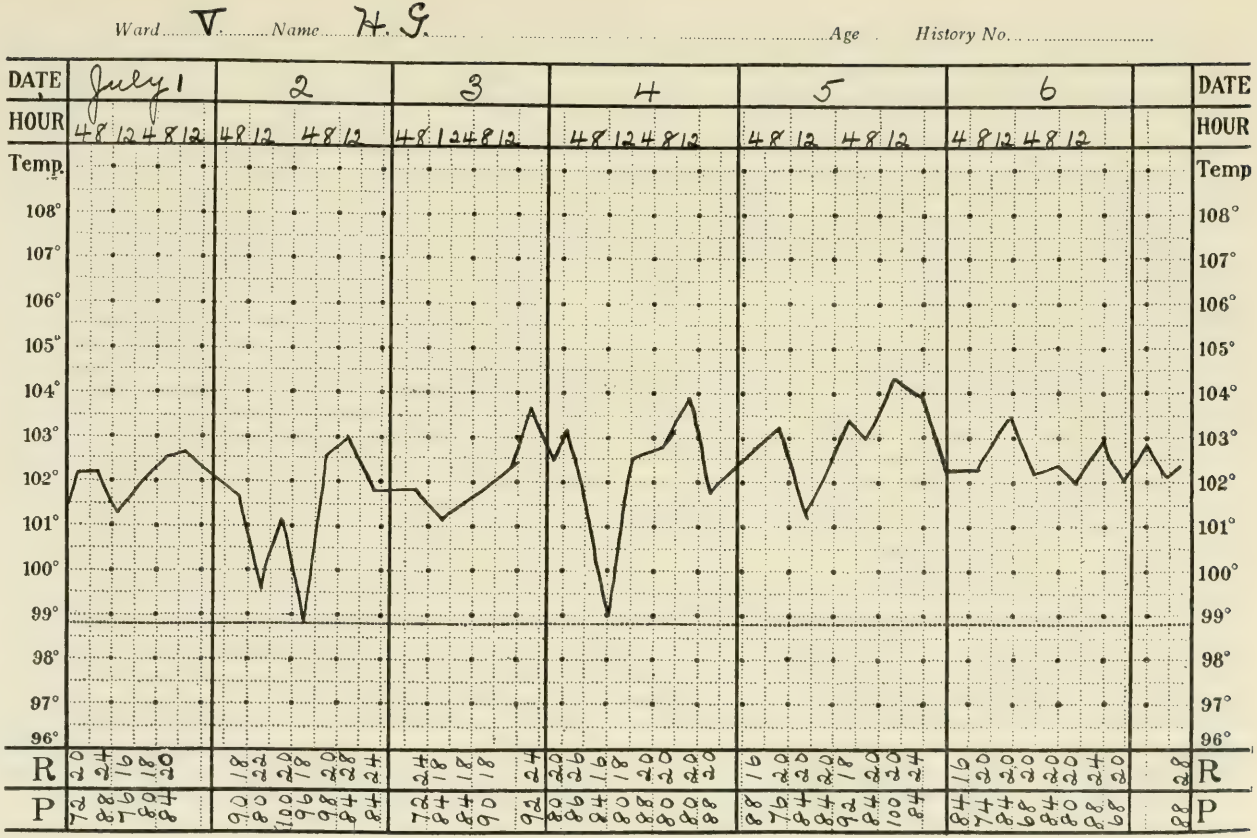
	June 23	June 29	July 6	July 7	July 17	July 19	July 22	July 26
Hemaglobin				50 %				
Red Cells				4,136,000				
Index				0.61				
Leucocytes	6,000	5,200	4,000	5,000	4,300	3,600	7,300	4,300
Polynuclears				80 %			97 %	
Large mononuclears				1.0			0.0	
Small mononuclears				18.0			3.0	
Eosinophiles				1.0			0.0	
Neutrophiles				0.0			0.0	

Autopsy: Acute general miliary tuberculosis.

It is to be noted that in this case we found the leucopenia regarded as characteristic, but with differential counts showing in one instance a definite increase of the polynuclear leucocytes, and in the other an overwhelming predominance of these cells.



Acute Miliary Tuberculosis—Typhoid Type.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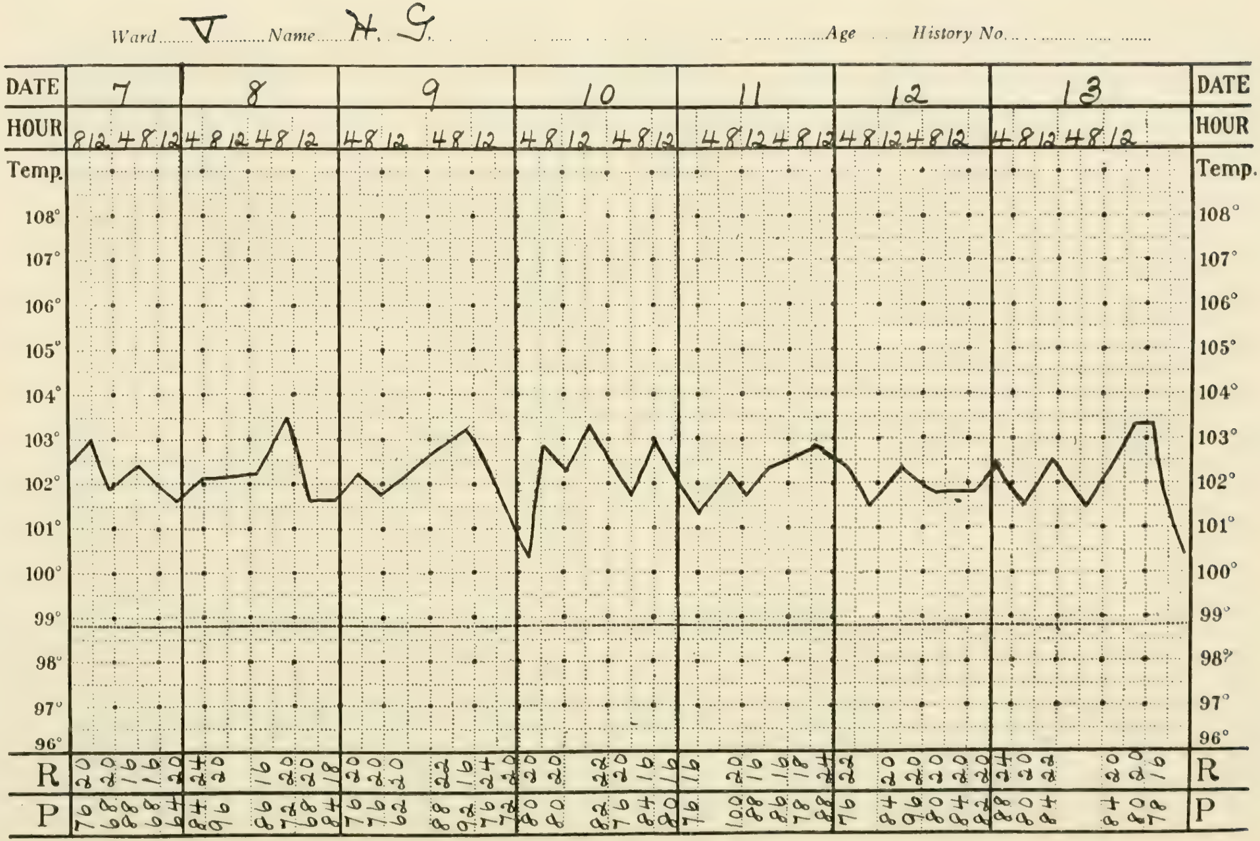
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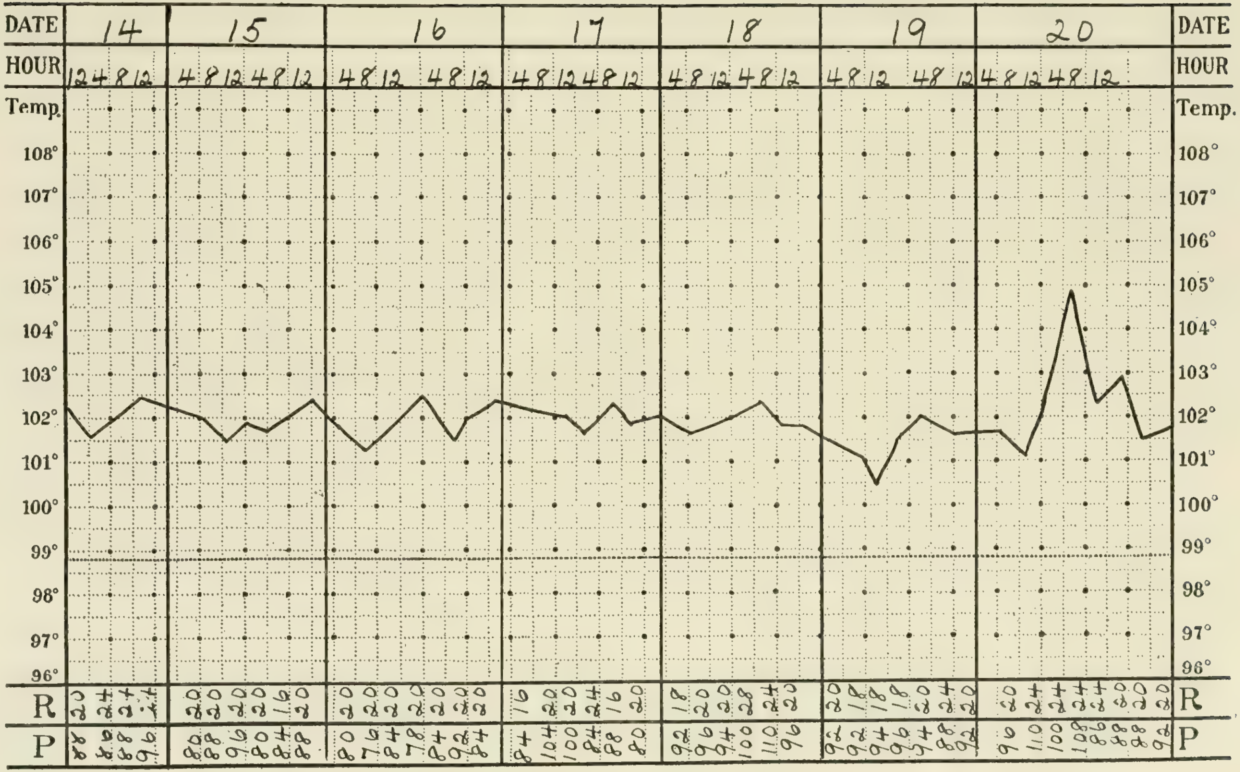

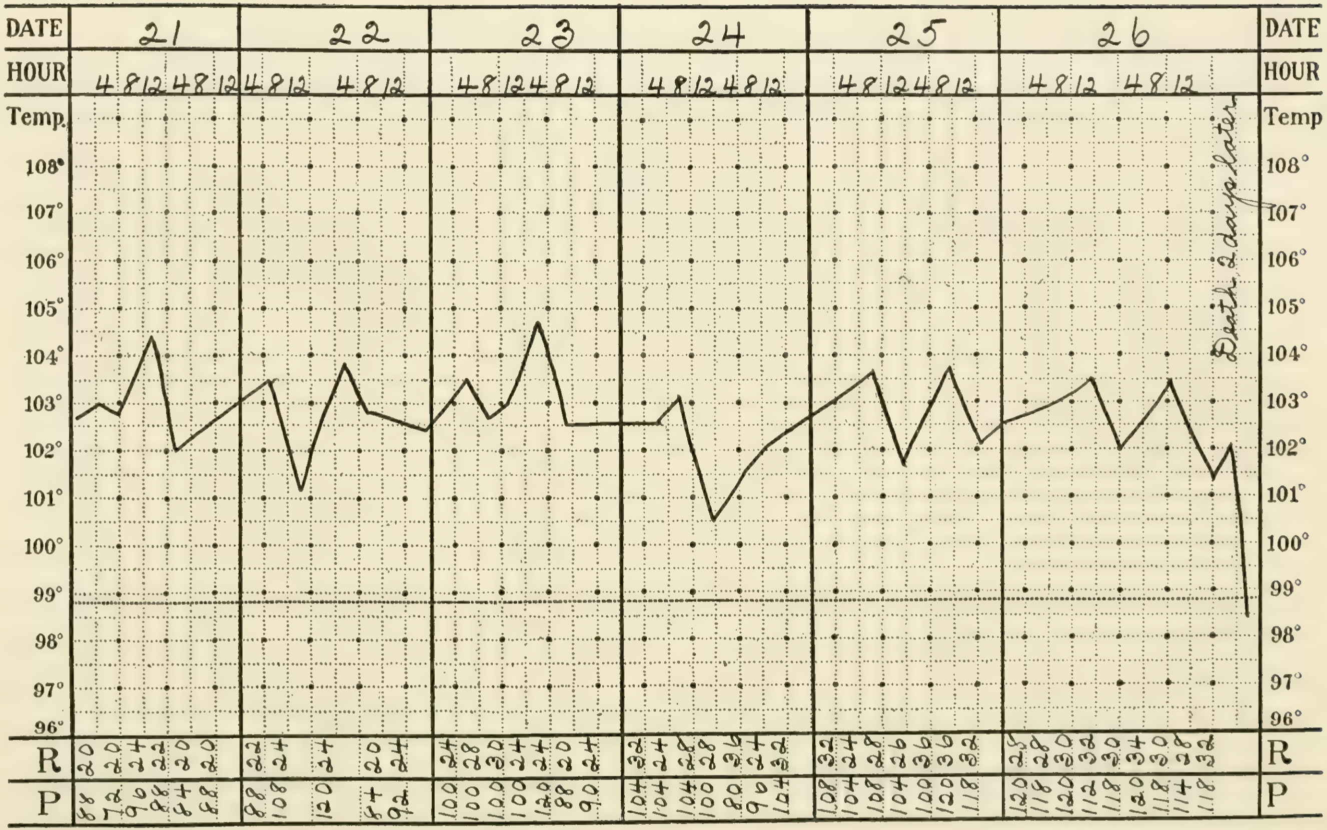
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Acute Miliary Tuberculosis—Pulmonary Type.

L. S., aged 20 years. Admitted April 3rd. Died June 24, 1906.

History: Family, good. Personal: Lived in British Guiana till 6 months ago, when she came to New York. Otherwise negative. Previous: Measles in childhood, whooping cough in childhood, dysentery in childhood, dyspepsia for 6 months. Present: For one week not well, "caught cold," tired and easily fatigued. Two days ago a chill, headache and fever. The same afternoon a second chill. In bed since onset. Complains only of fever, headache, prostration, anorexia and constipation. On admission, T. 102°, P. 102, R. 20.

Course: Continuous fever, 100°–102°–103°, rather irregular in type. Fever in all lasted three months. Pulse rather rapid, 80–100–120. Respiration, 20–30. In last weeks, 30–40. Gradual loss of flesh and strength and increasing anæmia. Always comfortable and cheerful.

Physical Examination: Entirely negative at beginning, except palpable spleen. April 30th, by Dr. Baldwin of Saranac—no pulmonary lesion. June 14, signs of a general bronchitis.

Opthalmoscopic examination by Dr. Parker: One small area in right eye suggestive of miliary tubercle.

In final weeks occasional cyanosis of fingers and lips, gradually deepening and becoming continuous.

Laboratory Tests: Widal always negative. Blood cultures negative. Cultures from feces negative. No malarial organisms in blood.

Urine: 1015–1025 Albumen, a faint trace—rarely casts, no pus.

Diazo reaction repeatedly positive.

BLOOD EXAMINATIONS.

	Hb.	R. C.	Index	White	Poly.	Trans.	Large	Small	Baso.	Eosin.
Apr. 3...	78	6,024,000	0.68	8,100	82.0	0.5	2.0	15.5	0.0	0.0
Apr. 4...	.....	....	.....	9,600	64.0	5.5	0.5	23.5	0.0	6.5
Apr. 7...	.....	....	.....	......	82.0	0.0	10.4	6.0	0.4	1.2
Apr. 23...	76	....	.....	13,800	84.5	1.0	3.0	10.5	0.5	0.5
May 6...	77	....	.....	16,100	.....	.....	.....	.....	.....	.....
May 8...	.....	....	.....	16,300	.....	.....	.....	.....	.....	.....
May 10...	.....	....	.....	......	72.0	3.0	8.0	14.0	0.0	2.5
May 12...	.....	....	.....	......	74.5	1.5	11.5	16.5	0.0	2.5
May 22...	.....	....	.....	10,500	82.0	4.0	2.0	7.0	0.0	5.0
June 8...	69	4,704,000	0.73	......	.....	.....	.....	.....	.....	.....
June 22...	.....	....	.....	19,000	.....	.....	.....	.....	.....	.....

Autopsy: Acute general miliary tuberculosis, the lungs crowded full of miliary tubercles.

Special attention is called to the variability of the leucocyte count, both absolute and differential. Out of seven counts only one, that of April 4, gave what is commonly stated to be the characteristic blood picture of acute miliary tuberculosis, an absence of leucocytosis, with an increase in the proportion of lymphocytes. The rapid variation of the differential counts indicates the need of great caution in interpreting the meaning of any one of them. The most careful examination of the lungs as late as April 30, more than a month after the onset, gave no signs, although at that time there must have been large numbers of miliary tubercles in the lungs.

The resemblance of the first type to typhoid is so close that for weeks a differential diagnosis is usually impossible. They have in common the fever, prostration, gradual emaciation, and slowly increasing anæmia. Each shows an absence of leucocytosis, or leucopenia, with usually an increase in the per cent. of lymphocytes. Either may give the Diazo reaction. Either may show moderate enlargement of the spleen. Either may have tympanites and diarrhœa. Miliary tuberculosis with intestinal lesions (ulcers) may even show blood in the stools. Either may give a Widal reaction. The resemblance is so close that in some cases a decision between them must be left to the autopsy.

In most cases, however, we can by care anticipate the conclusion. Acute miliary tuberculosis of this type looks like mild typhoid, but it may be distinguished by these points:

1. A previous tuberculosis of any part of the body.

2. The fever of miliary tuberculosis is more irregular than that of typhoid. It shows a greater daily variation; it may be low all of one day, to rise again the next; it more frequently shows sudden brief drops to normal or below with quick recovery.

3. When a typhoid of similar severity would be improving, the patient with miliary tuberculosis is stationary or still failing. Thus at the end of the third or fourth week the temperature instead of falling, continues or runs a higher course.

4. Hemorrhage from the bowels in any degree, although it may occur, is most uncommon in tuberculosis.

5. Of the decisive features of typhoid mentioned above, the roseola, the typhoid bacillus in the blood or excreta, are absent.

6. The possibility of the occurrence of a Widal reaction in tuberculosis, especially the acute miliary form, must be admitted. The reaction in these cases, while not altogether typical, so closely resembles that obtained in typhoid that even the most skilled observers find difficulty in distinguishing them and the inexperienced may see no difference. It still remains true that the repeated finding of the Widal reaction is more characteristic of typhoid than of tuberculosis. (See Wood: Chemical and Microscopical Diagnosis, p. 236).

The second (pulmonary) type of acute miliary tuberculosis is much like the preceding and presents the same difficulty of diagnosis for weeks. Then careful observation will regularly disclose some important points.

1. Attacks or periods of cyanosis of the lips (and other mucous membranes) and the finger tips. This cyanosis is at first slight and variable, quite definite at one time, then disappearing entirely for a time. It is not caused by any ascertainable disturbance of the circulation, the pulse remains the same. It is free from any distress on the part of the patient—in fact the comfort of the patient despite the definite cyanosis is quite notable.

2. The signs of diffuse bronchitis, which belong to both typhoid and tuberculosis in the early stages, instead of gradually clearing up as they should in typhoid, gradually increase. The expansion of the chest and its resonance are slowly and insidiously impaired, yet without definite areas of consolidation. It is often amazing at autopsy to find a lung packed with miliary tubercles, which have given no pronounced signs during life.

3. The periods of cyanosis become more frequent and longer until the symptom becomes permanent. The respiration quickens gradually, but to the end there is no real dyspnœa or distress.

4. The cough is always much less than the signs would lead us to expect, and may be absent even to the end. Similarly ex-

pectoration is most often lacking, and even when present does not show bacilli.

In connection with this question of the diagnosis of tuberculosis mention may here be made of the tuberculin reactions of Von Pirquet and Calmette. For some reason not yet satisfactorily explained both these reactions fail in acute miliary tuberculosis, so that they are not of value in the cases we are here discussing.

III. Septicemia—Cryptogenetic.

The third common cause of protracted fever, and in our experience much the most frequent one, is cryptogenetic septicemia. When we have to do with fever in association with suppurating wounds, an infected uterus, large abscesses, etc., the explanation of the fever is, of course, easy. In the group of cases to be here considered, however, the origin of the septicemia is not revealed, and the search for it is often vain.

The cases which belong in this group may be readily classified: 1. Blood infections—malignant endocarditis—pyogenic organisms found in blood. 2. Local infections—latent—no organisms in blood—symptoms produced by absorption of toxines from some hidden focus of suppuration which finally develops into a localized abscess, such as abscess of liver, perinephritic abscess, or empyema.

The following abstracts of cases illustrate these different types:

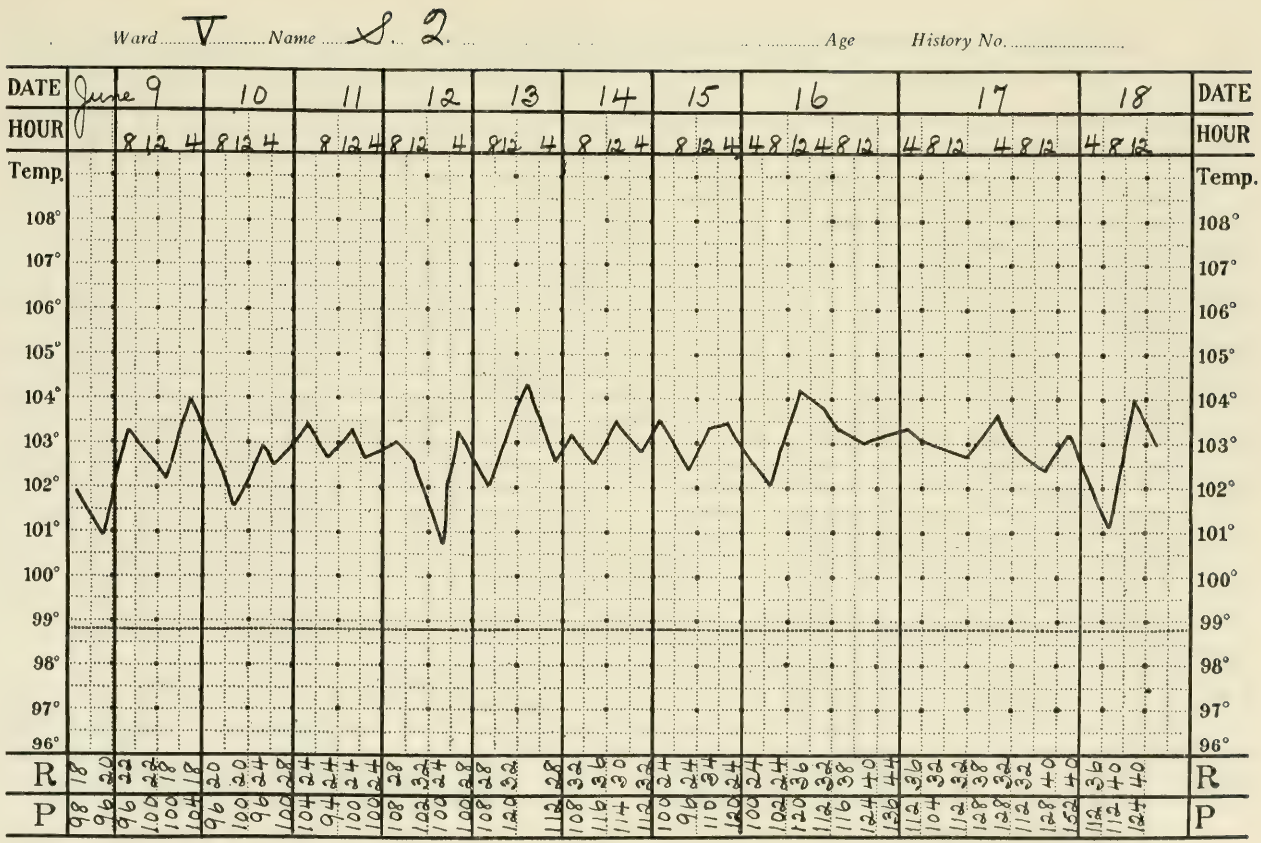
Malignant Endocarditis.

a. Acute type

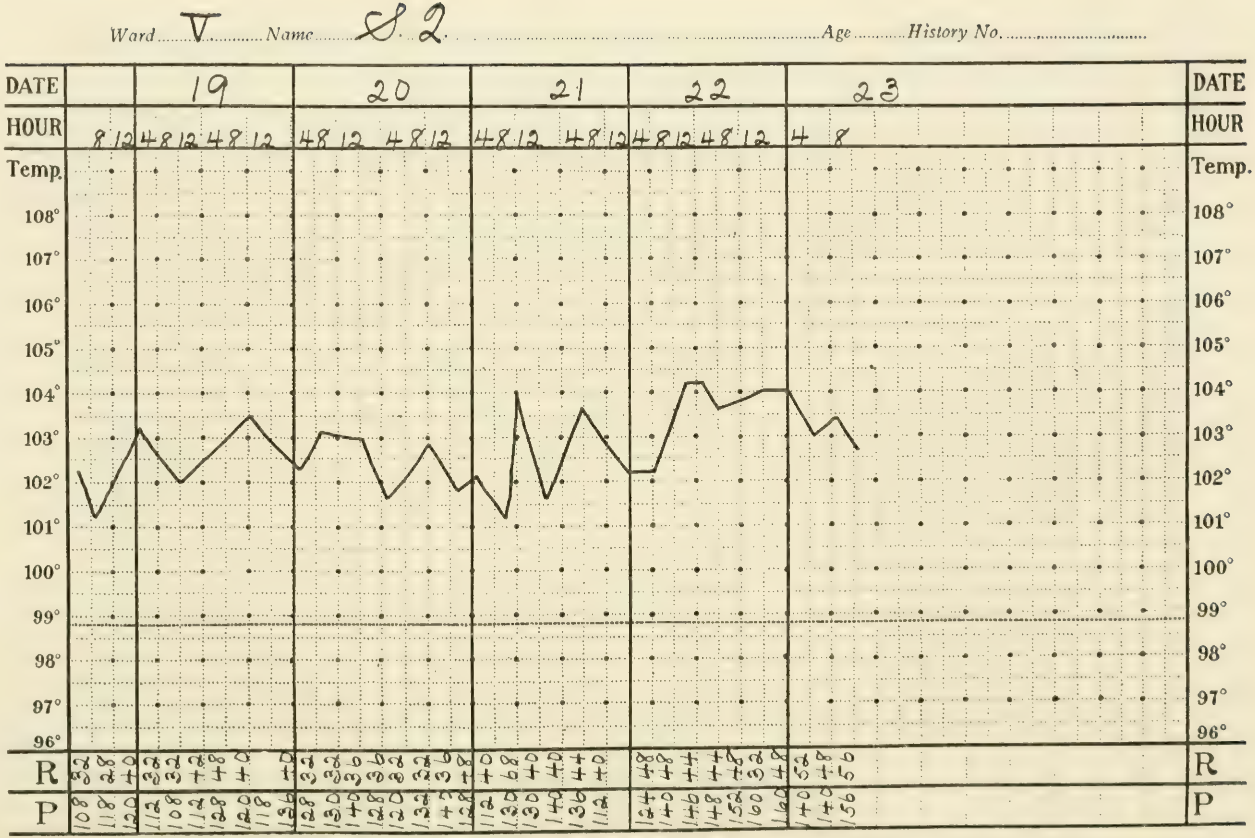
F. M., aged 11 years. Admitted Sept. 25, 1907. Died Oct. 1, 1907.

Previous history of chorea and rheumatism, pneumonia and measles. Present history: For ten days before admission she had had fever and headache and had occasionally been delirious. On admission her temperature was 103.8°, pulse 120, and respiration 48. The physical examination at this time showed marked apathy and prostration, a coated tongue, an enlarged heart with systolic murmurs at the base and apex, a rapid pulse, but of good quantity, the abdomen distended and tympanitic, and an enlarged and palpable spleen.

The leucocytes on admission were 15,200.



MALIGNANT ENDOCARDITIS—RESEMBLING TYPHOID.


Ward V Name S. 2. Age History No.
DATE
19
20
21
22
23
HOUR
8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8 12 4 8
Temp.
108°
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
R
P

The clinical diagnosis at this time was typhoid fever.

During the following six days the temperature was continuously high, ranging from 102° to 105°, the curve being altogether like that of a most severe typhoid fever. The pulse grew steadily more rapid and weaker and the apathy and prostration deepened. In a general way the course was that of a severe typhoid. But on the 29th, four days after admission, the leucocytes were found to number 31,500 and a differential count showed 87.0 polynuclears, 1% transitionals and the mononuclears, large and small, only 12%. On the same night a number of petechial spots appeared on the chest and side of neck. Later paralysis of the right side developed. The cardiac signs became more pronounced. Finally a blood culture taken three days after admission showed abundant growths of staphylococci.

The rise in the leucocyte count on the 29th showed that the case was no uncomplicated typhoid fever, while the rapid evolution of the petechial eruption and subsequent paralysis indicated clearly a malignant endocarditis.

The result of the blood culture confirmed this diagnosis.

b. Protracted or chronic type.

S. M., aged 19 years. Factory hand. Admitted Nov. 9, 1905. Died June 21, 1906.

History: Family, negative. Previous: Heavy lifting in room at high temperature. Malaria two years ago.

Present: For four months feeling poorly. Hands and feet cold, and chilly sensations at times. He had no dyspnœa, œdema, or shortness of breath. Bowels constipated. No nausea or vomiting. As he did not improve he went to a physician who told him he had heart trouble and that he had better stop work and take a rest. Since then he has been getting up late in the morning, and has rested much during the day, but without benefit. His chilly feelings continue. He has palpitation when he attempts to get about and is occasionally dizzy.

No dyspnœa. Marked anorexia, but no nausea or vomiting. No nose bleed or headache. Stools normal. All this time he has had fever and sweated a good deal at night.

Heart: Apex impulse maximum in IV space 2¾ inches to left mid line, an impulse can be felt in V space 3 inches to left mid line. Left limit of dullness corresponds. No enlargement made out. Action regular, forcible, not rapid. At apex there is a soft blowing systolic murmur transmitted to axilla and heard behind and also over whole precordium, being more accentuated over the pulmonic area. Basal sounds clear, the second pulmonic being the louder.

Pulse regular, a little rapid, good force and size, soft, wall palpable, markedly dicrotic, marked pulsation of arteries in neck. Examination otherwise negative.

Course: During the seven months of his stay in the Hospital this patient had more or less daily fever. At times the fever would be slight, but usually the temperature would at some time of the day reach 103°–104°. During the early weeks the fever was continuous, later it became irregular and much of the time intermittent in type. The condition of the heart remained the same throughout. The patient's friends finally insisted upon his removal from the

Hospital and the later history is not known. The more important features of the daily notes are as follows:

Nov. 25th: A systolic thrill at apex.
Nov. 29th: Spleen palpable.
Dec. 1st: Pain in left hypochondrium. Spleen large.
Dec. 15th: A few petechial spots on abdomen.
Jan. 1st: Murmurs the same.
Jan. 2nd: A few new petechial spots.
Jan. 15th: More petechiæ—on chest and back.
Jan. 22nd: Severe abdominal pain. Heart the same.
Jan. 26th: Pain in left shoulder.
Feb. 14th: From time to time new petechiæ appear.
Mar. 1st: Red blood cells in urine and tenderness over left kidney.
Mar. 14th: Temperature normal for several days.
Mar. 30th: Temperature not above 100° for two weeks.
Apr. 9th: Temperature not above 100° for two weeks.
May 16th: Temperature shows occasional rises to 102°.
June 7th: Fever irregular. Some burning pain on micturition and blood in urine.

	Hb.	Red Blood Cells	Leucocytes	Polynuclears	Large mononuclears	Small mononuclears	Transitionals	Eosinophiles	Basophiles
Nov. 9..	55%	3,200,000	6,200	......	......	......	......	......	......
Nov. 10	......	....	12,000	......	......	......	......	......	......
Nov. 20.	......	....	8,700	......	......	......	......	......	......
Nov. 28.	......	....	10,000	......	......	......	......	......	......
Dec. 22.	72	3,840,000	19,000	76.0	7.5	12.5	2.5	1.5	......
Dec. 29.	......	....	12,100	......	......	......	......	......	......
Jan. 2..	50	3,272,000	13,200	76.0	7.0	14.0	2.5	0.5	......
Jan. 9..	......	....	8,100	84.5	2.5	11.0	1.5	0.5	......
Jan. 15.	......	....	....	77.5	4.0	14.5	3.0	1.0	......
Jan. 24.	......	....	10,300	......	......	......	......	......	......
Feb. 12.	......	....	16,100	76.5	2.0	11.0	5.0	0.5	......
Mar. 6..	......	....	14,300	......	......	......	......	......	......
Mar. 30.	......	....	19,600	90.0	0.5	6.5	2.5	0.5	......
Apr. 16.	......	....	8,800	71.0	0.5	19.5	7.0	1.5	0.5
Apr. 24.	......	....	22,400	......	......	......	......	......	......
May 22.	......	....	9,400	......	......	......	......	......	......
June 16.	......	....	11,800	89.0	0.5	5.0	5.5	......	......

A blood culture on Nov. 28 was negative; a second on Dec. 28 yielded a pure culture of staphylococcus pyogenes aureus.

Urine 30–70 ounces, av. 50. Sp. gr. 1015–1020. Albumen, 24%–31%. Hyaline and granular casts. Rarely blood and blood casts.

Comparison of the results of the blood counts, especially the absolute and differential leucocyte counts, with those of the second case of acute miliary tuberculosis shows that the only notable difference lies in the more marked reduction of hemoglobin in the latter case. The leucocyte counts show closely similar variations both in totals and in the distribution of the several types.

ABSCESS PERINEPHRITIC.

J. M., aged 23. Iron Worker. Admitted June 3, 1907. Transferred June 18, 1907.

History: Family, previous and personal irrelevant.

Present: For three months complaining of bloating and pain in the abdomen; the latter not related to taking of food. For three weeks more or less vomiting of mucus. At one time he vomited a small quantity of blood. He has some pain low in the left side on deep breathing.

On admission T. 101.2°, P. 92, R. 21.

Physical examination at this time elicited nothing of importance. The patient looked as though uncomfortable, but was thought to be exaggerating his sufferings.

Course:—Fever continuous. 100° to 104°. Daily variation 2° to 3°, duration in all about one month.

Pulse 72 to 96.

Respiration 20 to 24.

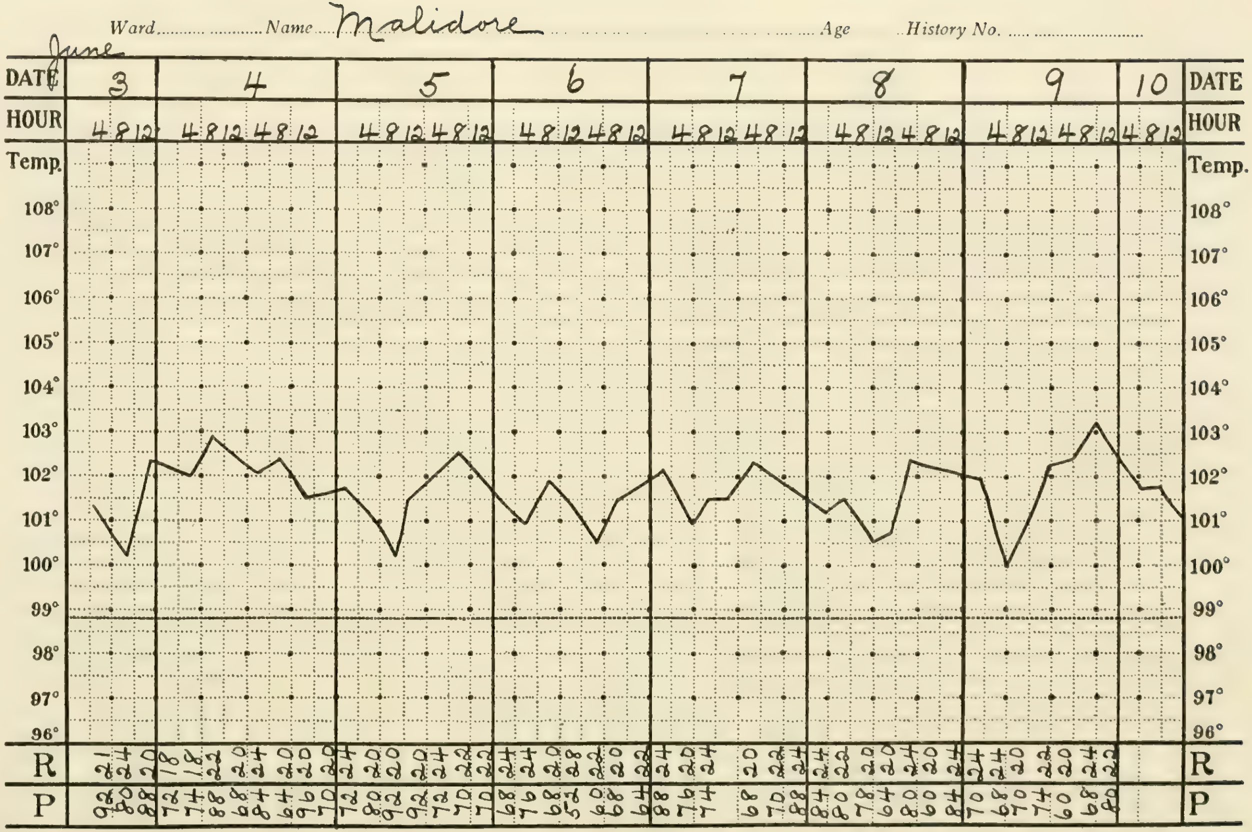
Leucocytes:

Jan. 4th, 14,200
Jan. 5th, 10,000

Hb	80%
Red Blood Cells	4,200,000
Index	1
Leucocytes	10,000
Polynuclears	77%
Large Mononuclears	7
Small Mononuclears	15
Eosinophiles	1
	100

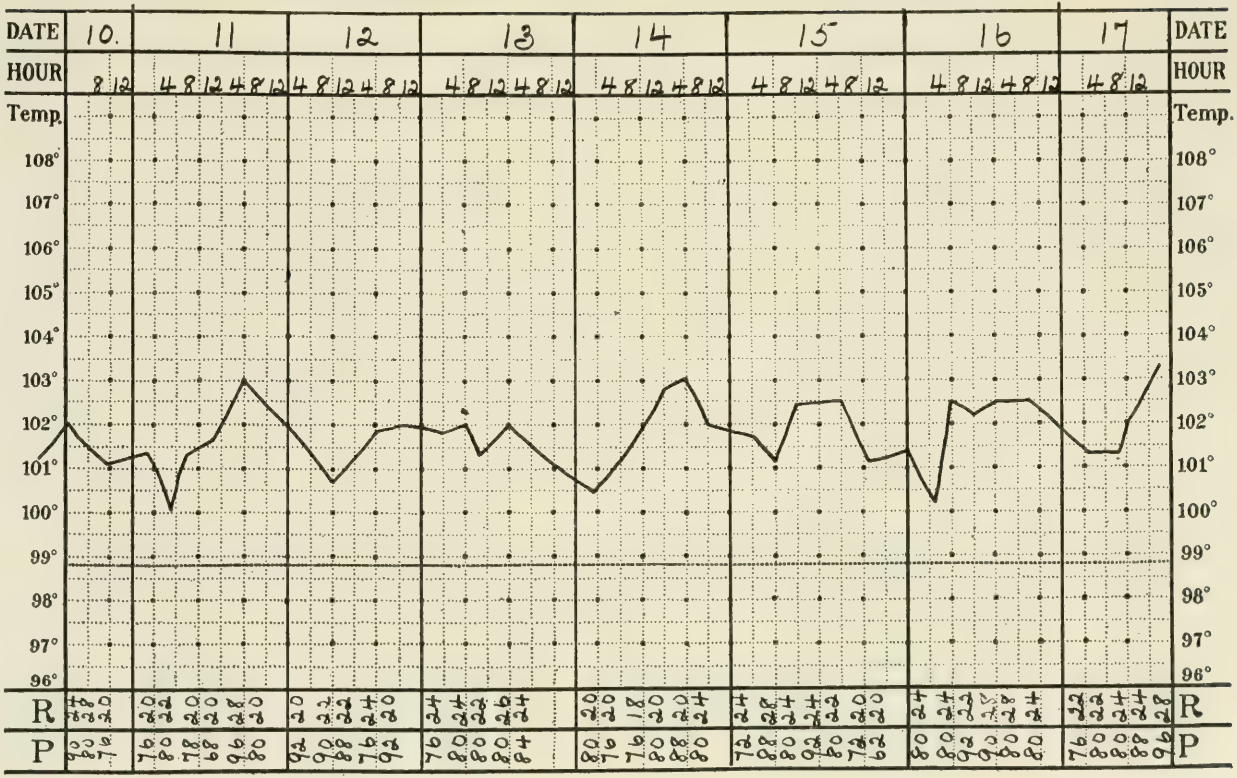
Jan. 8th, 10,600
Jan. 9th, 12,900
Jan. 12th, 17,100
Jan. 13th, 16,100
Jan. 16th, 23,100

At the end of two weeks the patient developed some swelling and tenderness in the iliolumbar region. He was transferred to the surgical side, and an abscess of some size, perinephritic, evacuated. Growths from the abscess showed



Perinephritic Abscess—Resembling Typhoid.

Ward .... Name Malidore .... Age History No. ....



micrococcus pyogenes aureus. He recovered promptly. Not until the development of the local signs was it possible to make the diagnosis.

Attention is called especially to the low total leucocyte counts had in the early weeks and the normal differential.

ABSCESS OF LIVER.

F. S., aged 35. Admitted May 6, 1904. Transferred June 13, 1904.

History: Family and previous personal history of no help.

Present: His illness began twelve days before admission with headache, malaise, and pain in the bones. Fever constant, from 103° to 104°. For one week some pain on right side on deep inspiration. On admission T. 100°, P. 96, R. 24. Physical examination at this time entirely negative.

Course:—A continuous fever ranging from 100° to 105°; daily variation of from two to three degrees, lasting about seven weeks before its origin was made out.

Pulse, 80 to 100. Respiration, 20 to 24.

Leucocytes:

May 6th,	19,300		
May 9th,	18,800		
May 15th,	17,500		
May 18th,	10,400		
May 19th,	12,200	Polynuclears	72.4%
		Large Mononuclears	7.6
		Small Mononuclears	18.8
		Basophiles	0.4
		Eosinophiles	0.8
			100.0
May 22nd,	15,200		
May 23rd,	16,500		
May 25th,	14,200		
May 27th,		Polynuclears	73%
		Lymphocytes	18
		Large Mononuclears	8
		Eosinophiles	1
			100
May 28th,	14,800		
May 30th,	13,600		
June 3rd,	14,200		
June 5th,	14,000		

Blood culture May 27th, no growth.

Urine, sputum and feces frequently examined without result. There gradually developed resistance in right upper quadrant of abdomen and some slight tenderness. He became weaker and more anemic; was transferred to surgical division and operation disclosed an abscess of liver.

In this case we note that after three fairly high counts the leucocytes sink to a rather indeterminate level and that both differential counts are normal.

SUBPHRENIC OR RETROHEPATIC ABSCESS.

J. L., aged 18 years. Oiler. Admitted Nov. 23, 1904. Transferred Dec. 22, 1904.

History: Family and previous history of no aid.

Present: He had had a cold and cough for some time. Three months ago he stopped work on account of abdominal pains, general in distribution, but most marked in umbilical region. Sometimes these pains shifted to the right side of the abdomen, especially if he slept on that side. The pains were most likely to come on after meals and were accompanied by bloating, but they also came when he was at work and interfered with his work. His appetite has been normal, his bowels very constipated. During his three months' illness, he has lost twenty pounds in weight and much strength. For at least three weeks of this time he has wakened nearly every night with fever and chilly sensations. At one time his temperature reached 104° according to his physician. The pain in abdomen radiates at times to chest and shoulder (right). On admission T. 99.8°, P. 92, R. 24. Physical examination at this time showed only a marked anemia—no cause for fever. Course: Intermittent fever from 97° to 104.8°. Frequent chills lasting at least 7 weeks before the origin was found. Pulse rapid with chills, but usually 80 to 90. Respiration 20 to 30.

LEUCOCYTES:

	Hb. Per cent.	Red Blood Cells.	Leucocytes.	Polynuclears. Per cent	Large mononuclears Per cent.	Lymphocytes. Per cent	Basophiles. Per cent.
Nov. 24	90		13,400				
Nov. 25			13,300				
Nov. 28	70	39,04,000	11,000				
Dec. 2			10,600	64	10	26	
Dec. 5			18,000				
Dec. 6			16,000	72	9	18	1
Dec. 8			14,300				
Dec. 10			14,600				
Dec. 14			16,500				
Dec. 16			9,100				
Dec. 17			9,600				

The patient gradually grew weaker and more anemic. To careful observation there seemed some slight enlargement of the right side in region of liver. There was occasionally a moderate epigastric tenderness, but the signs were so slight and variable that it seemed not wise to attach too great weight to them.

At one time on account of cough, expectoration of mucus, and a few localized rales it was thought that he must have pulmonary tuberculosis. We were finally, however, convinced that the trouble lay in the region of the liver. He was transferred and operated upon, an abscess being found posterior to and involving the right lobe of the liver. The patient finally died of exhaustion resulting from profuse hemorrhage from the liver wounds. Cultures from abscess yielded staphylococcus pyogenes albus.

Again we see that in the case of a suppurative inflammation the leucocyte count only once in eleven times rose to a level regarded as suggestive of pus. One of the two differentials suggested tuberculosis, the other was normal. In the early weeks of observation in the hospital tuberculosis seemed the most probable diagnosis. The gradual enlargement of the right side of the thorax, the marked anemia, rather frequent chills and sweating ultimately led to a correct diagnosis.

EMPYEMA.

F. D., aged 4 years. Admitted October 25, 1907.

History: Family, negative. Previous: Pneumonia 2 years ago and in Jan. 1907. Dry cough since. Attack of pain in right lower quadrant abdomen lasting one week in May, 1907. Present: Fever and pain in abdomen since October 6th. Occasional vomiting and cough. Pain agonizing at times. Chills repeated. On admission T. 103°, P. 144, R. 40.

Examination: Anemia—emaciation. Tenderness right side abdomen. Bulging of right lower thorax.

Course: Fever 104° to 98°—very irregular, lasting in all over a month, before the cause was found. Cough, vomiting, abdominal pain.

Leucocytes:

Oct. 25th, Hb. 65%	40,000
Oct. 26th,	31,000
Oct. 31st,	14,500
Nov. 8th,	22,700

Urine normal. Sputum—no Tb. No reaction to opthalmo-tuberculin test. Operation Nov. 9th. Localized collection of pus in right plura. Pleural culture, pneumococcus.

This case is reported with interest, for here the height of the leucocyte count and the course of the fever taken with the scant indication of an apparent enlargement of the right side of the thorax led to the suggestion that the boy had an empyema some time before physical signs justifying that diagnosis could be had.

In the Archives of Pedriatics, January, 1902, p. 22, Holt reports a case of high temperature for three months in a boy 2½ years of age, in whom the most careful study failed to disclose the cause of the fever. Briefly the symptoms were fever, varying from normal to 106.2°, a little cough, slight acceleration of respiration, progressive emaciation and exhaustion with varying signs over the lungs, never sufficient to justify the introduction of an exploring needle. At the autopsy which was made by the writer, we found two small sacculated empyemas, one on the right side situated on the diaphragmatic surface of the lung near its anterior border, the other on the left side at the base of the lung and close to the spine.

During the course of the fever the patient showed a leucocytosis varying from 10,500 to 28,000.

Delafield reports a similar case, the patient being a woman, whose fever lasted 234 days in all, and the empyema being found only at autopsy.

One should not leave the subject of protracted fever in children without remarking that in some instances the explanation is to be found in a suppurative pyelitis, the origin of which it may be quite impossible to explain. Difficulty in these cases arises only from failure to examine the urine. In young children especially on account of the difficulty of obtaining the urine the examination is likely to be omitted. The writer has seen one case in a child two years of age in which a fever ranging from 102° to 106° and persisting for three weeks was twice attributed by a distinguished consultant to a pneumonia which failed to appear. The examination of the urine at once showed an active pyelitis, and appropriate treatment promptly put an end to the fever. Instances of such cases running months before detection are on record.

Differentiation of These Forms of Septicemia.

Malignant Endocarditis.

In its typical form malignant endocarditis is easily recognized. The cardiac disturbance with presence of murmurs, the characteristic petechial rash, and the symptoms produced by the lodgment of emboli in various parts of the body make a clinical picture easily interpreted. In some cases, however, the cardiac symptoms are so slight as to be easily overlooked or undervalued, the rash and the embolic phenomena are absent for long periods of time, and the patient shows only an irregular fever, accompanied by increasing anemia and prostration. If limited to the interpretation of the clinical symptoms, we may well find it impossible to reach a definite diagnosis in such cases. But blood cultures will, as a rule, promptly clear up the mystery. A single culture may fail, but a second or third will almost surely detect the offending organism.

Of recent years we have had an unusual number of cases of malignant endocarditis in the wards of the Hospital, and the blood cultures have been regularly successful. With relation to the cases here reported, attention is called to the following points:

1. The absence of an indication, either in the history or in the body of the patient, of the source of infection.

2. The very irregular type of fever, and the long periods of comparative freedom from fever.

3. The marked anemia—progressive and accompanied by progressive emaciation.

4. The low leucocyte counts—although the blood may be swarming with pyogenic organisms.

5. The typical petechial eruption is of the greatest value in diagnosis. This eruption will often be found in the palpebral conjunctiva (lower lid); in some instances when it cannot be found elsewhere (Janeway).

6. The chronicity of the disease in some instances—6 to 9 months.

The Localized Abscesses or Suppurations.

In these cases the chief symptoms are those also found in Malignant Endocarditis.

1. Fever, very irregular in type. Sometimes repeated chills and sweating.

2. Progressive anemia and emaciation.

3. Absence of any indication of the locus of infection for weeks or months.

Blood cultures are, however, negative, and we may for long periods be quite unable to reach a satisfactory diagnosis, till at length the characteristic signs of a local suppuration or abscess develop. The duration of this period in these cases is quite striking. The empyema patient was under observation for a month, the perinephritic abscess gave a history of three months, the retrohepatic abscess of four months. Holt's patient was under observation for three months, and then the local collections of pus were found at autopsy. Delafield's patient lived 234 days.

The diagnosis presents the very greatest difficulties. Unless we may rely upon the ophthalmo-tuberculin test, we have at present no reliable means of differentiating these cases from those of miliary tuberculosis. In one of the series quoted the leucocyte count was high enough (40,000—31,000—23,000) to point clearly to a suppurative process, but in none of the others were the counts of definite value.

The differential counts upon which so much emphasis has of late been laid as a symptom of pus in certain localities are so variable that it is quite impossible to interpret them. We must in these cases rely upon unremitting vigilance for the detection of the signs of a definite abscess or suppuration.

INFLUENZA.

From time to time during the season when influenza is prevalent in the city, we see cases of continued fever in which the best explanation of the fever is the presence of an influenzal infection without local lesion. The following cases illustrate this type of fever fairly well, though both are relatively brief. In private practice it is not very unusual to meet such cases running for a month or more.

Case I. Miss S., thirty years. Admitted February 16, 1908. Discharged March 18, 1908.

February 16th. Entirely well until night. She had some muscular pain during night, and at 3 A.M. a hard shaking chill, followed by headache and severe muscular pains. No cough or expectoration.

Physical examination entirely negative. Leucocytes 11,500. Temp. 103°–104°. Pulse 110–120. Resp. 26.

February 17. Leucocytes 12,700. Pain in head and neck.

February 19. Temperature has been gradually falling and is now normal.

February 23. Yesterday without discoverable cause temperature rose again to 102° and patient again complained of headache and general soreness.

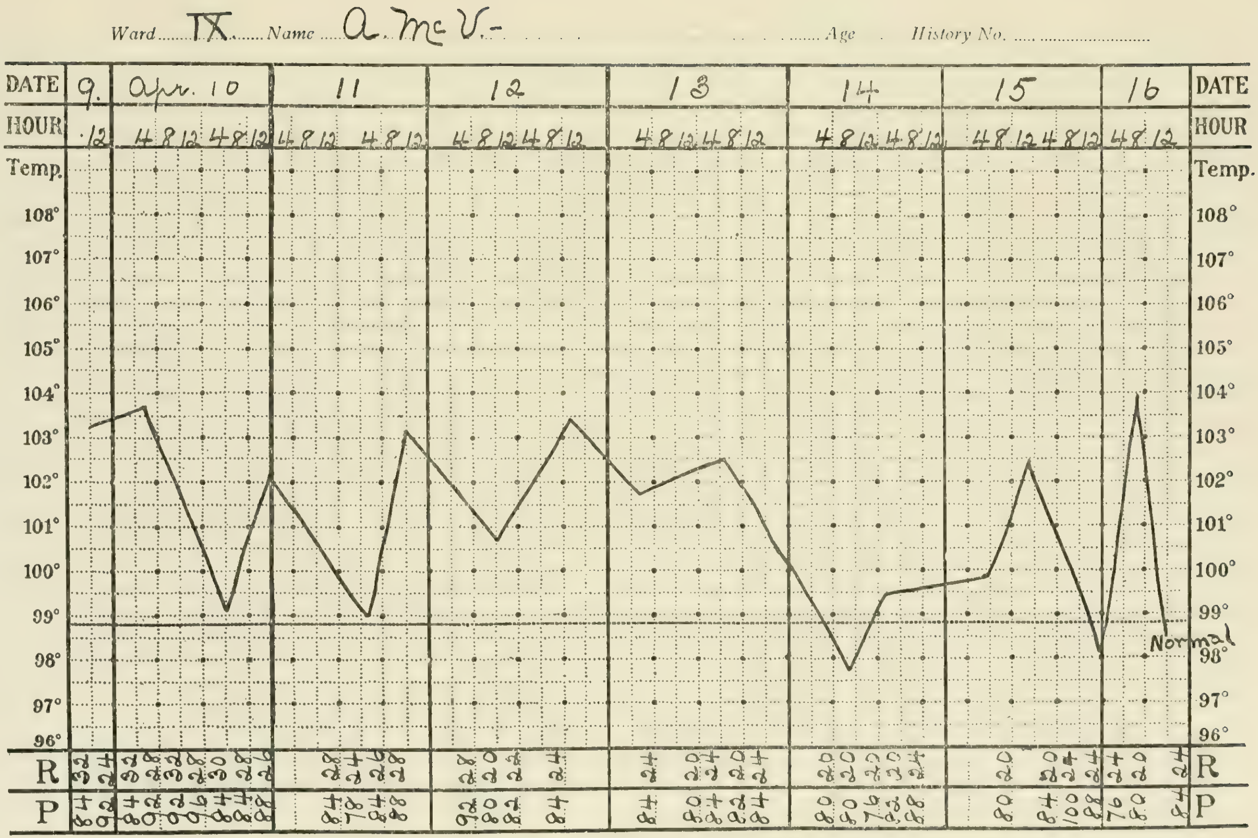
Physical examination negative. Leucocytes 15,300.

February 28. Another relapse with fever 101°, general malaise and soreness. A differential blood count is found normal. No malarial organisms.

March 7. After four days of normal temperature patient again has had a return of fever (102°) and all her previous symptoms. Leucocytes 15,000.

March 18. Since last note temperature has remained normal and patient has made a rapid recovery.

Case II. A. McV., twenty-three years. Bricklayer. Admitted April 9, 1906. Discharged April 27, 1906.


Ward IX Name A. McV.- Age History No.
DATE
9.
Apr. 10
11
12
13
14
15
16
HOUR
12
4 8 12 4 8 12
Temp.
108°
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
Normal
R
P

INFLUENZA.

April 3. Moderate frontal headache, anorexia, constipation, general soreness, prostration, cough with mucous expectoration.

April 5th. Severe epistaxis. Pain in shoulder and knees.

April 6th. Severe epistaxis. Chilly feelings, profuse sweats, pain in right chest.

April 8th. Fever reached 104°.

April 9th. Admitted to Hospital. Face flushed, tongue clean, patient looked sick, but physical examination showed nothing more. Temp. 103.8°. Pulse 92. Resp. 24.

April 11th. Feeling better. Some general soreness still. Cough with free mucous expectoration. Temp. 99°-103.3°.

April 13th. A small area of consolidation found in right middle lobe. Temp. 101°-103°.

April 15th. After remission for 48 hours temperature rose suddenly to 102.5°. Pharynx congested. Inguinal glands swollen. No cause found for increase in fever.

April 16th. Second sudden rise of temperature to 103.5°. No cause found.

April 27. Temperature remained normal after last note and patient made a rapid recovery.

The recognition of these cases is not, as a rule, difficult. They belong to the winter season, when influenza is prevalent.

They begin suddenly, usually with the characteristic symptoms, headache, general muscular soreness and pain, prostration. They may have a cough and expectoration, and in the sputum the influenza bacillus may be found in large numbers.

It is now well understood that this presence of the influenza bacillus is not a frequent happening in the affection clinically known as influenza. The great majority of such cases do not show the influenza bacillus, but show pneumococci, streptococci or staphylococci in large numbers in the sputum, if there is expectoration. Of course, also many of the patients have no cough or expectoration. When, however, the organism can be found in the sputum in large numbers, the finding is of significance.

The most characteristic feature of these cases is the exceeding irregularity of the temperature curve as indicated in both these cases. The fever comes and goes in a most unaccountable manner. It is to be understood that the most careful watch must be kept to exclude the presence of complications which would explain the sudden rise and fall of the fever, such as acute otitis, mastoiditis, or involvement of the antrum or accessory sinuses. We must also recognize the fact that the fever may come and go independently of such complications. Regularly with the return or increase of the fever there is return or increase in the clinical symptoms. These patients regularly recover. In protracted cases in private practice we often find that the best thing to be done for such patients is to get them out of the city.

The blood examinations in these cases have only moderate value, usually they show a slight or moderate leucocytosis ranging from 10,000 to 20,000.

The differential counts as in case 2 are all normal. Blood cultures are negative.

UNEXPLAINED FEVER.

The history of this patient is as follows:

M. S. G., aged 30. Admitted May 10, 1907. Discharged Jan. 1, 1908.

History: Family, negative.

Personal: Born in Scotland, in Honolulu 4 years, in Trinidad 1 year.

Menstrual: Amenorrhea 15 months.

Previous: Measles, typhoid, dengue, tuberculosis 3 years ago, tonsilectomy, appendicectomy.

Present: Cough, expectoration, constipation, nausea and vomiting. Headache, syncope, increasing weakness. Abdominal pain and fever from January up to admission.

Physical Examination: Negative except for a slight tenderness of left lower quadrant of abdomen.

Course: From May to June 1st the patient did well. She had one or two temporary rises of fever, but most of the time the temperature was within normal limits. All her symptoms cleared up, and except for constipation she felt well. From June to October she ran a continued fever of varying degree, for some days ranging from 100° to 101°, but most of the time higher, 101°–102°–103°.

There was an undulation very suggestive of typhoid in the weekly curves, but none of the characteristic signs of typhoid developed. There was almost constant leucocytosis, as the appended table will show, no Widal reaction, and negative blood cultures. The only suggestive thing about the physical examination was persistent tenderness over the left half of the abdomen, especially in the region of the left kidney. The urine was normal, an uncontaminated specimen was obtained and found sterile. The fever, leucocytosis, and persistent pain suggested a local suppuration, but the signs did not develop, and the patient's condition remaining good, action was deferred. Finally, in the first week of October the fever gradually rose, and on the 10th reached 105°. With this rise there was a distinct increase in the local tenderness and pain, and an exploratory operation seemed demanded. This was done by Dr. McCosh, and a most thorough examination of the abdomen disclosed nothing abnormal whatever. Lest by any chance a minute focus in the kidney should be overlooked, the kidney was exposed through a lumbar incision and carefully examined. No lesion found. The wounds were then sutured and the patient returned to the ward. The temperature at once fell and within three days became normal and so continued. The patient rapidly regained her strength and in a few weeks left the hospital quite well.

BLOOD EXAMINATIONS.

	Hb.	Red Cells	White Cells	Polynuclears	Transitionals	Large Mononuclears	Small Mononuclears	Basophiles	Eosinophiles
May 10	70%	5,600,000	15,100	76.5	3.5	10.5	8.3	0.8	1.0
June 9			23,800						
June 10			25,000						
June 24			15,300						
July 27			28,000						
July 31			16,500						
Aug. 2			18,900	84.	6.	2.7	7.3	0.	0.
Aug. 12			13,000						
Aug. 13			12,100						
Aug. 22			10,000						
Oct. 1	70%	4,500,000	25,000	90.	1.	6.	8.	0.25	0.25
Oct. 4			17,000	76	1.	2.	20.	0.	1.
Oct. 9			16,800						
Oct. 10		Operation							
Oct. 29			15,000						

For this case we have at present no satisfactory explanation. The symptoms, the blood counts (note the high percentage of polynuclears), the course of the affection indicated the presence of some purulent focus. No such focus was found, yet the patient promptly recovered after operation. There was no suggestion of hysteria in the patient. Mentally she was entirely normal.

Theoretically it may be possible that a minute focus of suppuration did exist in some part of the abdomen and that the circulatory changes induced by the operation brought about its cure, in some such way as laparotomy cures tubercular peritonitis; or possibly a minute focus was evacuated without detection.

Practically the case illustrates the fact that there are seen from time to time cases of protracted fever which cannot at present be satisfactorily classified.

Summary.

1. Malarial fever is easily recognized by the presence of the characteristic micro-organisms in the blood, and by its amenability to quinine. Fevers not conforming to these requirements are not malarial.
2. Typhoid fever can be recognized or excluded with equal accuracy by the combination of clinical and laboratory evidence.
3. Tuberculosis and sepsis of certain types present clinical pictures so closely similar that they can often only be differentiated by the ultimate outcome of the case, possibly only by autopsy.
4. Influenza may give rise to protracted fever which can usually be easily recognized from the conditions under which it occurs, sudden onset, characteristic symptoms and course.
5. Sepsis in other cases may be clearly indicated by very high leucocyte counts with high polynuclear percentages before any localization of the process can be made out.
6. Blood cultures are of very great value in the differentiation of fevers, especially in typhoid, and in such conditions as malignant endocarditis.
7. There are cases of long protracted fever which cannot at present be satisfactorily classified.

V.

PHAGOCYTIC IMMUNITY.

By J. C. Meakins, M.D., Resident Pathologist.

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In 1895 Denys and Le clef[1] made the observation that the serum of animals immunized to virulent streptococci was necessary for the phagocytosis of these organisms *in vitro* as well as in the body. They found that normal serum was powerless to produce ingestion of virulent streptococci by the leucocytes. By further experiments[2] they came to the conclusion that the serum acted upon the bacteria and not upon the leucocytes as previous workers had thought. Later Leishman[3] devised an ingenious method for the demonstration and estimation of phagocytosis. While working with this technique Wright[4] has demonstrated beyond doubt that the serum acts upon the bacteria, preparing them for phagocytosis, and furthermore has shown that normal serum contains a certain amount of the substance necessary for phagocytosis. To this body he has given the name "Opsonin."

By a comparison of the number of organisms ingested by the leucocytes in the presence of serum to be tested with the number ingested in the presence of normal serum, Wright has established what he has called the "Opsonic Index." By this method a quantitative difference between the normal and abnormal serum may be determined up to a certain point, but the factor of error is so great and the difference of the end reaction so slight that the results of its use have been very unsatisfactory. It is impossible by this method to demonstrate an opsonic power of serum comparable with that of the bactericidal power.

If a blood serum were shown to have a bactericidal power of four times normal it would be of little importance; yet up to the present time phagocytic activity four times normal has been seldom recorded by the opsonic index.

Phagocytic immunity may be many times normal, but the present technique does not afford us a means of determining such increase. Neufeld and Hüne,[5] closely followed by Klien,[6] have independently shown that there does exist a true phagocytic immunity in animals which have been infected with non-lethal doses of certain living organisms, and they have devised a means whereby it may be demonstrated.

Dilution of the blood serum, so successfully employed in the quantitative estimation of the bactericidal and agglutinative powers, has been thought by few workers applicable to the estimation of the phagocytic substances. It was by this means that Neufeld and Hüne first demonstrated a power to promote phagocytosis, quantitatively comparable with the other properties of immune serum.

Their technique is closely allied to Wright's, but they have found that by progressive dilutions a point can be reached where the opsonins disappear. In the present work I have closely followed their procedure, which I shall briefly outline.

The blood serum is collected in the usual manner both from the patient or animal infected and from a normal individual of the same species. The leucocytes are also collected as in Wright's work and a suitable emulsion of the infecting organism is prepared. The blood serum is then diluted to various strengths, which may reach one part in one thousand or higher, if necessary. Then capillary pipettes are prepared as described by Leishman, and equal parts of diluted serum, leucocytes and bacteria are mixed and incubated at 37° C. for a definite length of time, varying with the organism used. At the end of this period smears are made and suitably stained. In addition to the pipettes containing immune and normal serum, one is prepared by substituting 0.85

per cent. salt solution for the serum and treated as described above. The average number of bacteria per leucocyte in the preparation with salt solution is taken as the degree of spontaneous phagocytosis. The preparation made with the most diluted serum, which shows approximately this number, is taken as the point where opsonins have ceased to be active. If, for example, the preparation with salt solution shows a phagocytic average of 0.5 bacteria per leucocyte and all the dilutions of serum up to 1 in 600 materially exceed this figure, then the phagocytic power is taken as 1 in 600, or as 600, which shall be the manner of designation in the following experiments. The dilution of 1 in 600, in this case, is produced by diluting the serum 1 in 200, and then by mixing together equal parts of diluted serum, leucocytic emulsion and bacterial emulsion the serum is again diluted threefold, a final dilution of 1 in 600 being obtained.

The results obtained with the serum of a rabbit immunized to tubercle bacilli are cited for example:

Salt Solution—0.45 bacteria per leucocyte.

Dilution.	Bacteria per leucocyte with serum of normal rabbit.	Bacteria per leucocyte with serum of immune rabbit.
1 in 3	7.	8.
1 in 30	.29	9.
1 in 150	.4	6.
1 in 300	.43	1.6
1 in 600	.5	.35
1 in 1200	.2	.4

In this case the ordinary opsonic index would have been 1.1. With the method of dilution the opsonic power of the normal serum practically ceased below a dilution of 1 in 30, while the phagocytosis with immune rabbit's serum did not equal that with salt solution until a dilution of 1 in 300 at least was reached, that is, more than ten times the normal. Occasionally instances are met with where the normal serum causes greater phagocytosis than the immune serum in the undiluted state, yet the latter may show a much greater power when diluted, as the following protocol will demonstrate:

Salt Solution—0.6 bacteria per leucocyte.

Dilution.	Bacteria per leucocyte with serum of patient with typhoid fever on tenth day of disease.	Bacteria per leucocyte with normal serum.
1 in 3	10.	14.
1 in 30	6.8	.7
1 in 150	5.6	.5
1 in 300	.8	.9
1 in 600	.5	.6

Another point of interest which has been frequently observed is the apparently increased opsonic power of the diluted over the undiluted immune serum. Such increase is seen in the following protocol:

Salt Solution—0.7 bacteria per lèucocyte.

Dilution.	Typhoid bacilli per leucocyte with serum from patient recovering from typhoid fever.	Typhoid bacilli per leucocyte with normal serum.
1 in 3	9.	10.5
1 in 30	9.	.8
1 in 150	14.	.6
1 in 300	10.5	.65
1 in 600	4.3	
1 in 900	.9	
1 in 1200	.6	
1 in 1500	.65	
1 in 1800.	.7	

In the greater part of the experimental work performed on animals for the production of opsonic immunity bacterial vaccines have been used, and the results have failed[7] to show the production of an immunity of a high degree.[16] When, however, the infectious diseases in man have been closely imitated by the injection of living organisms in an attenuated form or in non-lethal doses very striking results have been obtained. The injection of living Bacillus typhosus,[6] Bacillus paratyphosus and the vibrio of cholera[5] has produced marked opsonic immunity.

In the following experiments living organisms have been used; and in all instances save with Bacillus tuberculosis the injections have been subcutaneous, since this method of inoculation seems to produce a better reaction than intraperitoneal or intravenous inoculation. Realizing that the different groups of bacteria may produce varied forms of immunity I have selected members of the different classes of bacteria most common in the causation of infectious diseases in the human subject.

Acute infections:
- I. Bacilli (producing bactericidal immunity).
  - (a) B. dysenteriæ of Flexner.
  - (b) B. dysenteriæ of Hiss.
- II. Pyogenic Cocci.
  - (a) Staphylococcus aureus.
  - (b) Streptococcus pyogenes.

Chronic infection.
- Bacillus tuberculosis.

BACILLUS DYSENTERIÆ.

Experiment I. On June 25th, 1907, one loopful of Bacillus dysenteriæ, Manila, type Y, was injected subcutaneously in a rabbit. This dose was repeated at intervals of from five to sixteen days, and gradually increased until on August

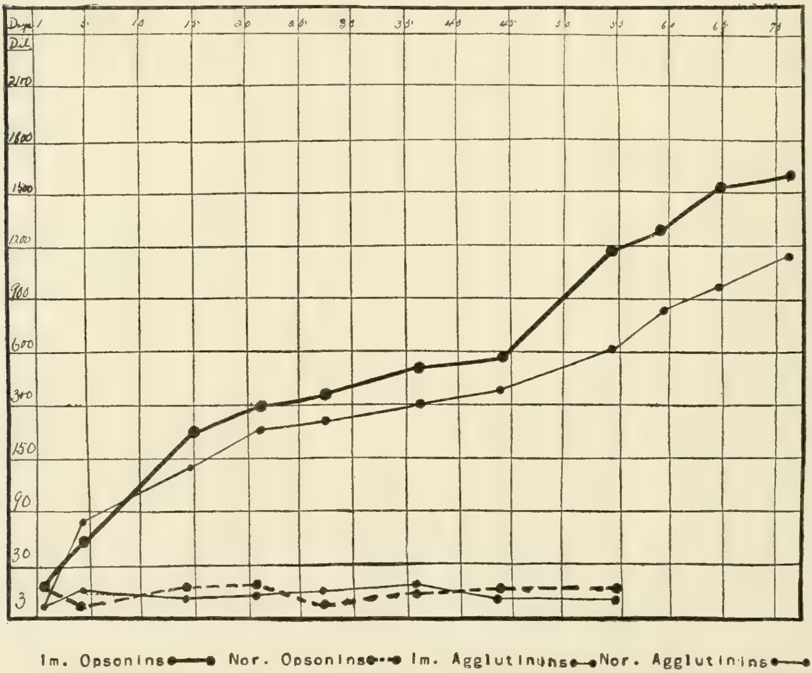

Chart I. Bacillus dysenteriæ, Manila, type Y.

29th two-thirds of an agar slant was injected. During this period the opsonic and agglutinative power of the rabbit's serum was estimated and controlled by normal serum and salt solution. The microscopic technique was employed for the estimation of the agglutinins and the length of time before the result was taken was one hour. In the estimation of the opsonic power the preparations were incubated for eight minutes, as a longer time produced marked degeneration of the intracellular organisms. The slides were stained with Hastings' modification of Jenner's stain and fifty leucocytes counted in each. This experiment is demonstrated by Chart I.

The highest opsonic power in the normal serum was 10, while the opsonins in the immune serum rose to 1600. The highest agglutinative power of the normal was 10 and of the immune serum was 1100.

EXPERIMENT II. In this case Bacillus dysenteriæ, Manila, type (Flexner), was used for immunization, and doses similar in size and frequency to those of the preceding experiment were employed. The animal was under observation from June 26th to September 5th, 1907, or seventy-two days.

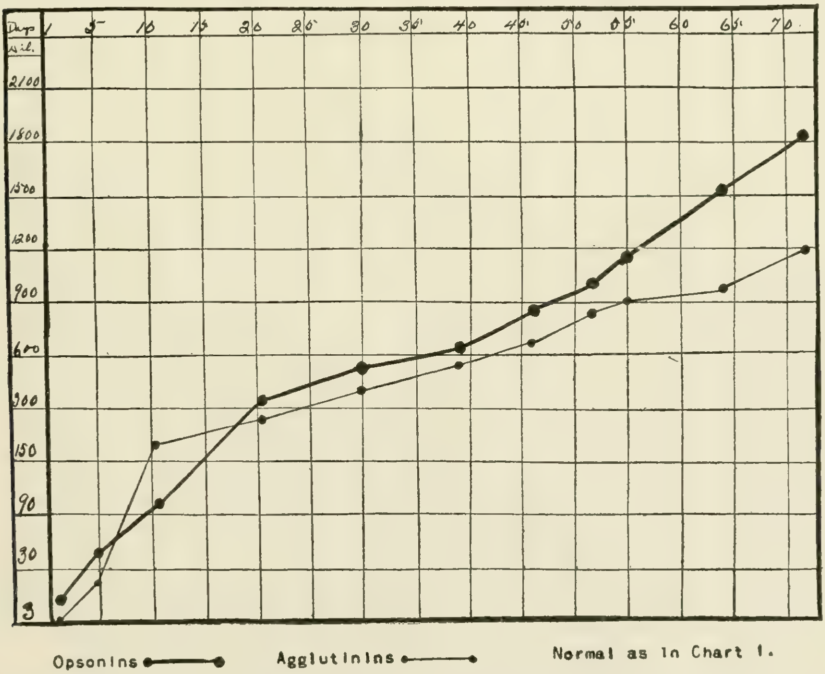

CHART II. Bacillus dysenteriæ, Manila, type (Flexner). The curves indicating normal opsonins and agglutinins are identical with those of Chart I.

The result of the last experiment (Chart II) was very similar to that of Experiment I. The highest opsonic power was 1900 and the agglutination reached 1200, while the normal agglutinins never exceeded 10.

In examining the results of these two experiments the production of phagocytic immunity to the dysentery bacillus is evident, and the close parallelism between the opsonic and agglutinative curves suggests that there may be a relationship between these two bodies.

Experiment III. A rabbit was immunized to Bacillus dysenteriæ (Flexner) as in Experiment II, but was under observation for a much longer period, namely, 144 days. In this experiment, besides the opsonic and the agglutinative power, the bactericidal power was estimated. The technique of the estimation of the bactericidal power was that of Neisser[8] as modified by Stern and Korte[9] and later by Klien. The serum of a normal rabbit was frequently examined to determine for comparison its content of immune bodies. The following table shows the maximal dilutions in which positive results were obtained.

Agglutinative power	1–10?
Phagocytic power	1–10
Bactericidal power	nil

For the first 98 days the opsonic, agglutinative and bactericidal powers all gradually increased as shown in Chart III. But at this period the animal developed an abscess of the abdominal wall at the site of inoculation; from the pus, Staphylococcus aureus was cultivated. It was not found necessary to incise this abscess which disappeared spontaneously. For a period of 16 days (March 14th to 30th) on account of unavoidable circumstances I was unable to inject the animal, and during this period it lost a little weight and did not seem as well as usual. Its general condition gradually grew worse after this date and the animal died on May 5th, '08. On March 18, '08, the phagocytic power was 1,300, the bactericidal power 950, while the agglutinative power was slightly lower. After this date and synchronous with the illness of the animal the opsonic and bactericidal power quickly dropped towards normal. Two days before death the former was 60 and the latter 30. On the other hand the agglutinins progressively increased, and just before death reached their highest point, namely, 950.

The autopsy was performed one hour post mortem. The animal was much emaciated, and the viscera showed only cloudy swelling. There was no abscess formation and the intestines appeared normal. Cultures from the heart blood, liver, spleen, lungs, and kidneys gave Bacillus dysenteriæ in pure culture.

An analysis of Chart III gives a very good idea of the immunity

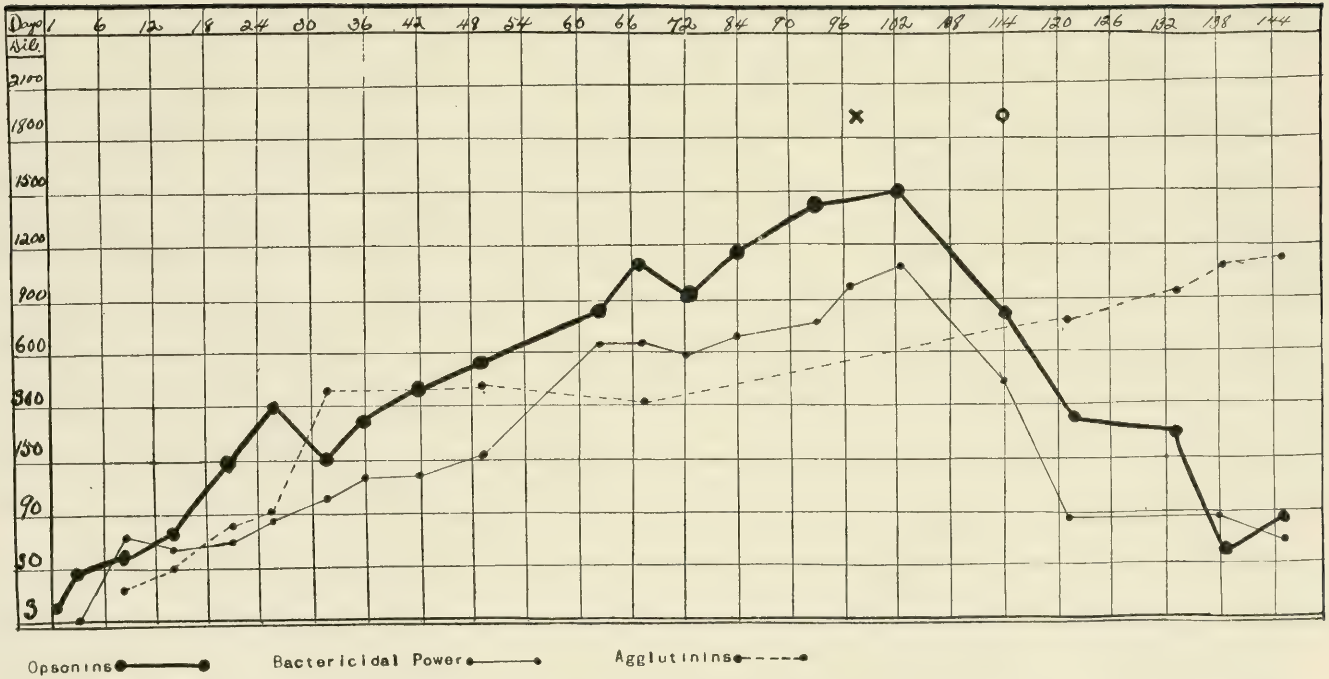

Chart III. Bacillus dysenteriæ (Flexner). Curves indicating normal opsonins and agglutinins are identical with those of Chart I. X = March 14. O = March 30.

produced in animals by the inoculation with living cultures of Bacillus dysenteriæ and allied organisms. An absolute comparison between phagocytic and bactericidal power by the technique used, is obviously impossible. The parallelism between the opsonic and bactericidal curves is evident, and affords some evidence that the opsonins are related to the amboceptors, but later experiments will demonstrate the fallacy of this assumption.

The parallelism of the curves of the agglutinins and opsonins observed in Experiments I and II was again found up to a certain point. Nevertheless the great divergence of the curves after March 30 is against the view of some authors that these bodies, which are in common specific and thermostabile, are related or identical. Experiments with other organisms will still further demonstrate that the agglutinins and opsonins do not always run parallel courses.

In the low dilutions of the highly immune sera the agglutinins may have produced a favorable condition for phagocytosis, since agglutination occurs very quickly, and the leucocytes can readily find clumps of opsonized bacteria. But in spite of this fact, when the agglutinins were still increasing, the opsonic curve steadily decreased. On the other hand, with the high dilutions, for example from 700 to 1300, the agglutinins exerted no power in one hour, whereas the opsonins were very active in eight minutes.

The cause of the animal's loss of weight and illness after March 30th, '08, is hard to explain by facts admitting substantial proof. It seems probable that just prior to this date the animal was exerting all its powers of immunity to withstand the infection repeatedly administered but the demand for immune bodies became greater than the supply, and a drop of the opsonins and bactericidal power occurred between March 18th and 30th. The inoculation on this date accentuated this depression, which became more marked with each subsequent injection.

The great importance of the phagocytic and bactericidal substances in the protection of the body against infections is very well demonstrated in this experiment. Even when these bodies are being produced in large amounts by the animal organism, continued increase in the amount of infection may overwhelm the supply and lead to rapid consumption of the immune bodies which have lost mastery over the infection, or actual diminution in their production may result. An example of an analogous condition is relapse in typhoid fever, occurring in the presence of a highly bactericidal serum. Diversion of complement could not have been the cause of the progressive decrease in the bactericidal power noted in Experiment III, as normal rabbit's serum was always added to the mixture, which was tested, and on several occasions the usual amount was doubled in order with certainty to satisfy with complement all the amboceptors which might be present.

Agglutinin without the presence or aid of the other bodies of humoral immunity, appear to have little importance as a protective agent in infections due to Bacillus dysenteriæ. The phenomenon of Eisenberg and Volk,[10] which gives evidence of the presence of agglutinoids, or proagglutinoids according to Shiga,[11] was observed in these experiments in the low dilutions. The continued increase of the agglutinins until death has shown that prognosis may be unfavorable even though they are abundant, and accords with the frequent observation of relapses or recurrences in typhoid fever, although the serum shows high agglutination.

The increase of the bactericidal power and agglutinins in these experiments coincides with similar increase found by Shiga in horses when inoculated with the Bacillus dysenteriæ.

The conclusions which may be drawn from this series of experiments are as follows:

I. A high opsonic power may be developed against the bacillus of dysentery.

II. The bactericidal and opsonic powers of the serum may decrease when the agglutinative power is increasing.

III. A close parallelism has been observed between the quantitative changes of the opsonins and amboceptors occurring with immunization to Bacillus dysenteriæ.

Staphylococcus Aureus.

Experiment IV. On December 17th, 1907, one-half an agar slant of Staphylococcus aureus, obtained from a case of cellulitis, was heated to 65° C. for one-half hour and injected into a rabbit. This injection was followed in seven days by all of the growth from an agar slant, similarly heated. These inoculations were given with the hope of producing some immunity before living organisms were inoculated. The result in this animal was very satisfactory, and subsequent inoculations produced no local suppuration. The injections of living organisms were given at intervals of from four to six days, beginning with one loopful and increasing the dose slightly with each inoculation. Unfortunately the animal was pregnant and abortion was produced; and a severe mixed infection of the genito-urinary tract followed. The animal was killed after it had been under observation for a period of forty-four days. The autopsy showed no other lesion but that mentioned above. The kidneys contained large abscesses and the uterus formed a bag of pus. Cultures were taken from the bladder, uterus and kidneys, and in all instances there was a growth of Staphylococcus albus, streptococcus and a bacillus giving the reactions of Bacillus coli.

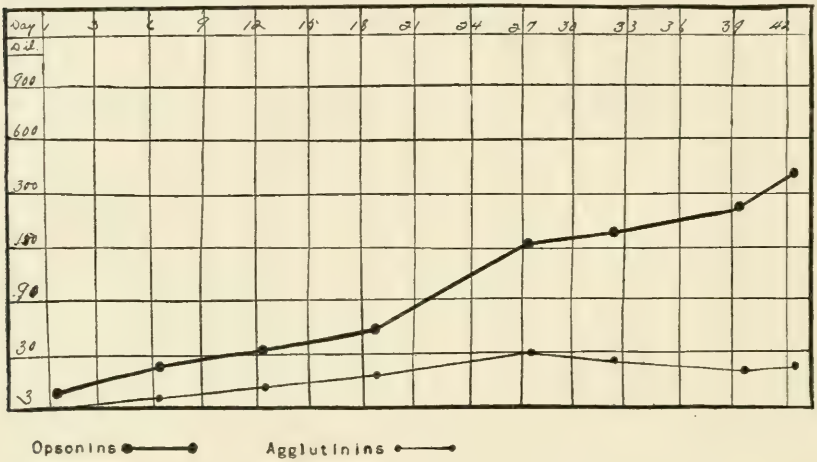

Chart IV. Staphylococcus aureus.

The opsonins and agglutinins were estimated during the time the animal was under observation. Controls made frequently with the serum of a normal rabbit have shown that these bodies are normally present, but never active in a dilution above 1 in 10, and sometimes they are not active even in this dilution. The technique was similar to that employed in the first set of experiments, with the exception that the preparations were each incubated for fifteen minutes instead of eight. The serum of the inoculated animal revealed a marked increase in the amount of opsonins. At first the reaction was slow, but later progressed more rapidly, and at the time of death the opsonic activity was 400, or forty times the normal. The agglutinins, however, never rose above 30, and this point was only reached on one occasion.

In no experiment was any intra or extra-cellular lysis of the organisms noticed, and at all times the cocci stained very well and no shadows were seen.

Further experiments with staphylococci were unsuccessful, as the animals developed abscesses at the points of inoculation and frequently pyæmia resulted. Nevertheless from the one observation just recorded it appears that phagocytic immunity of a fairly high degree can be produced against Staphylococcus aureus, and further evidence will show that phagocytic immunity plays an important rôle in the destruction of the pyogenic cocci.

STREPTOCOCCUS PYOGENES.

The strain of streptococcus used in this experiment was obtained in blood culture from a fatal case of malignant endocarditis and pyæmia of short duration. It was very virulent to mice, killing them in small doses in twenty-four hours.

EXPERIMENT V. On May 24th, '08, this animal was injected with one-half the growth from an agar slant culture of streptococci. The dose was irregularly increased, inoculations being given at intervals of from five to nine days. The animal was under observation for a period of ninety-seven days, and during this time the opsonic, bactericidal and agglutinative powers of the blood serum were frequently estimated. The technique was similar to that described for Staphylococcus aureus, but it was found of greater advantage in the plating for the bactericidal experiments to use blood agar plates. These were prepared by adding 1 c.c. of sterile defibrinated beef blood to 10 c.c. of melted agar at 42° C. Control plates were always made to be sure that the culture media were sterile.

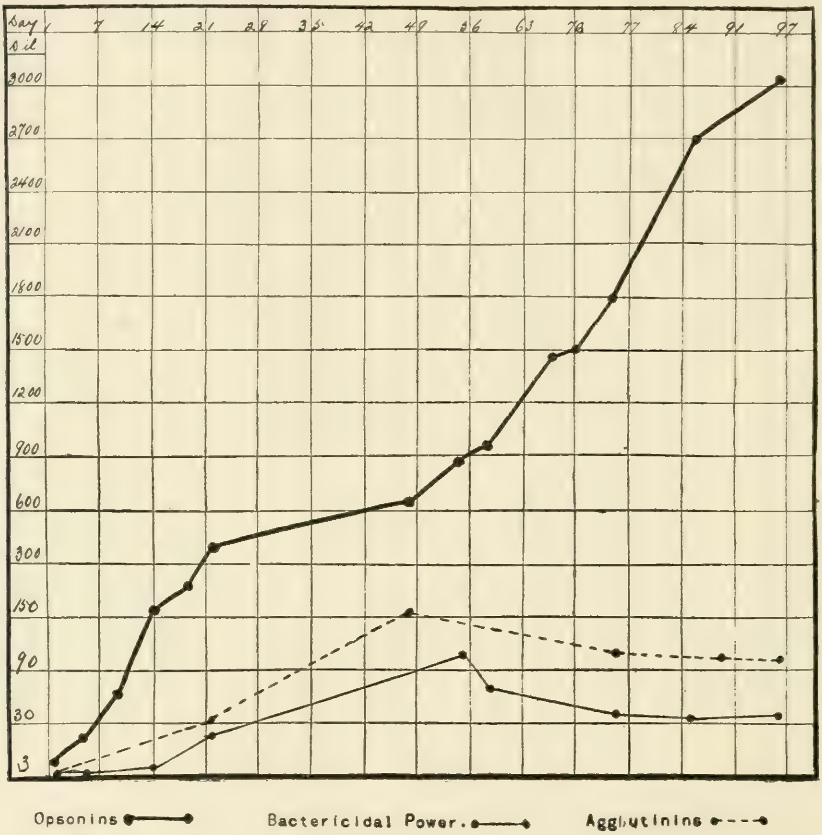

CHART V. Streptococcus pyogenes.

In this medium the colonies of streptococci could be readily counted as they were surrounded by a small zone of hæmolysis.

Experiments were made with normal serum and the following results were almost constantly obtained:

Bactericidal power	0
Opsonic power	10
Agglutinative power	0

The results of these experiments are graphically demonstrated in Chart V.

The highest point reached by the bactericidal power was 100, and this level was reached only on one occasion. In fact the bactericidal power seldom rose above 30, and the power of agglutination was slightly higher. The end reaction for both of these bodies was very unsatisfactory, except in very low dilutions. In fact when the experiments were carried out in duplicate, the results were often very indefinite.

The estimation of opsonins, on the contrary, had a definite result; opsonins steadily increased in quantity until an opsonic activity of 3000 was obtained. The extra-cellular cocci showed no degeneration even when the serum had the greatest power. On the other hand when the animal had developed an opsonic power of 600, degeneration of the intracellular organisms was first observed. This degeneration became more marked as the opsonic power increased, but at no time did the bacteria exhibit the degree of degeneration found in the experiments with Bacillus dysenteriæ.

The high degree of opsonic immunity developed in this animal is strong evidence that phagocytosis is the most important factor in the destruction of streptococci. It confirms the observations of Neufeld and Rimpau,[12] who have found that phagocytosis is very active in the destruction of strepococci *in vivo*, whereas bactericidal power, although increased, plays a minor part. Ruediger,[13] however, when working with the serum of patients suffering from erysipelas, found that the opsonic power was but slightly increased above normal and the bactericidal power was absent. He gives details of but one observation of the phagocytic power and the method of estimation is somewhat similar to that employed in the above experiments. Although the bactericidal power may not be greatly increased in infection with streptococcus, I agree with Neufeld and Rimpau that it is present; bactericidal substances are probably present in small amounts, but the opsonic power plays the greater rôle.

Neufeld[14] has demonstrated that agglutinins are produced in animals immune to streptococci, although seldom present in a dilution over 1 in 100. On one occasion he reports their presence in a dilution as high as 1 in 500. In the present experiments the highest point reached has been a dilution of 150; this fact corroborates the previous observations. The lack of parallelism between the curves of the opsonins and amboceptors in this experiment is a strong argument against their identity. An attempt to explain the absence of bactericidal power by deviation of complement would be useless, as abundant complement has been added in each experiment, and bactericidal bodies at no time gave any indication of material increase.

There is likewise an entire lack of parallelism between the opsonins and the agglutinins in the immunity produced in rabbits to Staphylococcus aureus and the Streptoccocus pyogenes.

The conclusions that may be drawn from these experiments are as follows:

I. A high degree of opsonic immunity to Streptococcus pyogenes and Staphylococcus aureus may be produced in rabbits.

II Opsonins are more important than the other known immune bodies in causing protection against the pyogenic cocci; in rabbits immunized to Streptococcus pyogenes bactericidal substances and agglutinins are produced in small amounts and apparently play a minor rôle in the active immunity against this organism.

III. Opsonins are not identical with the amboceptors of the bactericidal substances.

Bacillus Tuberculosis.

For investigation of phagocytic immunity in experimental tuberculosis the selection of the strain of bacilli to be employed is of great importance. The organism must not be of high virulence. Through the kindness of Dr. Opie I obtained from the Rockefeller Institute for Medical Research a strain of tubercle bacilli which was even in large doses not fatal to rabbits, and the animals recovered although they showed for a short time signs of infection. The animal was subsequently inoculated with a second strain of greater virulence in order that the immunity produced by the attenuated culture might be tested.

The emulsion of tubercle bacilli employed for the estimation of the opsonic power was killed by exposure to direct sunlight for twenty-four hours, and then ground up in a small test tube with a glass rod under aseptic precautions as described by Sellards and Jeans.[15] In this manner a very satisfactory emulsion was obtained; it was free from clumps and fragmentation of the bacilli was very slight. The preparations were incubated for fifteen minutes and the smears were stained in carbol fuchsin at 37° C. for twelve hours, decolorized in 95 per cent. alcohol for ten minutes and counter-stained with Loeffler's methylene blue for five minutes. This method stained the leucocytes very distinctly and gave them a clear outline; there was little of the destruction which occurs when greater heat or when acids are employed. One hundred leucocytes were counted in each slide, instead of fifty as in the preceding experiments.

Experiment VI. On August 9th, 1908, a rabbit received into the ear vein 2 c.c. of an emulsion of non-virulent tubercle bacilli. The emulsion was opaque, and was freed from clumps by first grinding the bacilli very carefully and then centrifugizing the emulsion until the supernatant fluid was cloudy but contained no visible particles. The opsonic power was estimated as described above and controlled with normal serum and salt solution. Normal sera always showed an absence of phagocytosis at 30; in fact its strength may have been much less, as dilutions between 3 and 30 were not made.

In the treated rabbit the opsonic power decreased below normal for a week after inoculation but suddenly began to increase, and this increase steadily progressed until a power of 1,500 was reached forty-four days after the original inoculation. There was then a slight drop, and the animal was again inoculated on October 3, 1908, fifty-three days after the first injection. On this occasion an emulsion of the virulent culture was prepared by the method described above and the intravenous method was used for inoculation. The opsonic power continued to fall slightly, but eleven days after the second inoculation it had regained its high point of 1,500.

During the period of observation the animal was frequently weighed and the curve of weight closely followed the opsonic curve; at first there was a sudden loss of weight, followed by a slow recovery until the original weight was exceeded. After the second inoculation there was no drop in weight corresponding to that following the first injection.

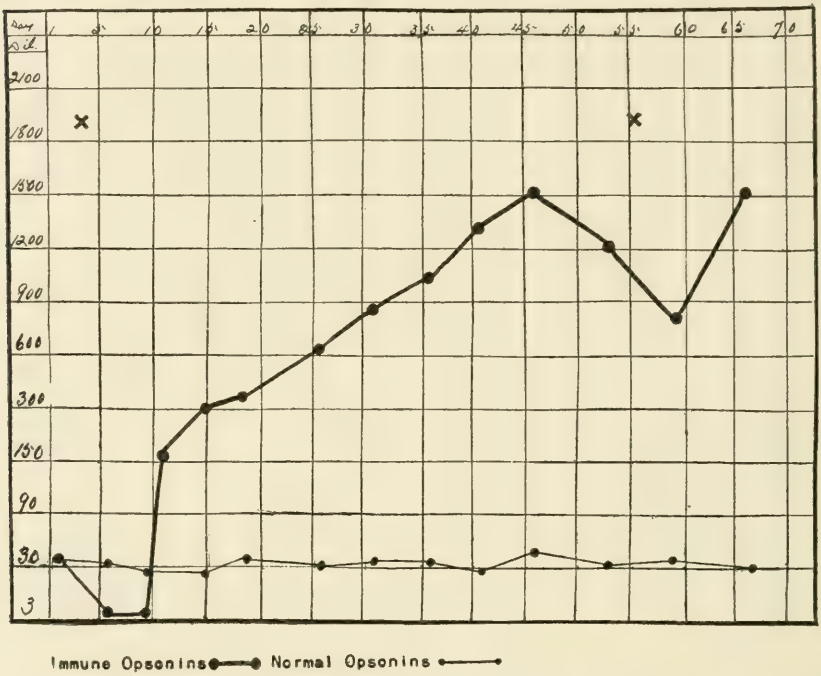

CHART VI. Bacillus tuberculosis. X, X = inoculation.

As no satisfactory method has yet been devised whereby the bactericidal power against the tubercle bacilli can be estimated, a comparison between this body and the opsonins is impossible. In none of the experiments was any lytic action on the extra cellular organisms seen, though occasionally in the low dilutions of the most powerful sera an increased beading of the bacilli seemed to have occurred, but the change was too indistinct to justify a definite opinion concerning the lytic action of the serum.

Observations made by several workers indicate that agglutinins occur with tuberculous infections, but they are not found in large amounts.

The drop in the phagocytic power after each inoculation was most likely due to the demand for a greater quantity of protective bodies than the body was capable of providing, and the amount present in the serum was temporarily reduced; but the animal was in such good condition that the loss was soon replaced. As the inoculation was not repeated the increased demand did not continue, whereas in Experiment III inoculations were repeated and the animal finally died. That this drop in the opsonins may have been the "negative phase" described by Wright is probable.

The animal used in this experiment is rapidly gaining weight twenty-eight days after it received an inoculation with virulent tubercle bacilli sufficient to cause death if the animal had not developed immunity from the first injection.

It has been stated above that there is at present no evidence to show the development of a bactericidal immunity in tuberculosis. Observations of several workers indicate that development of agglutinins in tuberculous infections is limited. It is therefore reasonable to suppose from this experiment that opsonins play an important part in tuberculous immunity.

The following conclusions may be drawn from the experiment just described:

I. Animals immunized with living tubercle bacilli may develop phagocytic immunity of a high degree.

II. Such immunity may help to protect the animal from a lethal dose of virulent tubercle bacilli.

With slight modification the method used in these experiments is applicable to routine clinical observations, and might, as suggested by Klien, be used as a means of diagnosis. The further application of this method of observation may add greatly to the knowledge of the phenomenon of phagocytosis, especially in those infectious diseases of man in which phagocytic immunity is known to play a more or less important part.

In conclusion I wish to express my sincere thanks to Dr. Opie for his valuable aid and advice in this work.

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VI.

SUPPURATIVE PERICARDITIS.*

By Ellsworth Eliot, Jr., M.D., of New York.
SURGEON TO THE PRESBYTERIAN AND GOUVERNEUR HOSPITALS.

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The literature of purulent pericarditis has been admirably collated by Roberts and C. B. Porter. By the former surgeon 37 instances of operation for that condition were tabulated from different sources in 1897, and to that number 10 additional cases, reported in the literature between 1897 and April, 1900, were added by Porter. In the present instance the rarity of this condition fully warrants the publication of a case of this kind recently under the writer's observation, while, at the same time, an opportunity is afforded for brief mention of those cases that have been published since Porter's contribution in 1900.

An anaylsis of cases of suppurative pericarditis hitherto published shows that in the great majority of instances this condition is secondary to some distant focus of infection, while only exceptionally is the infection either introduced directly into the pericardium or of unknown origin. Thus in 19 of Roberts' series of 39 cases is a history of a focus of infection in either the lung or pleura, or both; in 6 others the primary focus consisted of an acute osteomyelitis; in four others (as in the writer's case), the original infection could not be traced, while in only three instances the pyo-pericarditis was the direct result of a penetrating wound. In many of the secondary cases the pyo-pericarditis was only one of a number of metastatic purulent foci such as are commonly associated in a condition of general sepsis. Closely associated with the etiology is the prognosis, and it is needless to say that the prospect of a cure after operation is much more favorable where the infection is limited to the pericarditis sac than where the pyo-pericarditis is a part of a general sepsis. That occasional recoveries are secured, however, in this latter group of cases, certainly warrants surgical interference under all circumstances where the patient is not moribund, as the only chance of averting a fatal issue.

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The pathological changes in pyo-pericarditis are interesting and important. Usually the entire pericardium is converted into an abscess cavity, the heart, according to Brentano, being displaced downward and forward against the chest wall, a position in which exploratory puncture may readily penetrate one of its chambers. Occasionally, as in the writer's case, the heart is more deeply seated and not likely to be damaged by the exploratory needle. Exceptionally, the pericardium may be subdivided into several distinct abscess cavities, as in the case of Delorme (mentioned by Roberts), and of Coutts and Rowlands. Such a condition is favored by adhesion of the heart to the anterior pericardium, the abscess cavities being situated laterally and posteriorly. The character of the purulent exudate varies. In the early stages, especially after infectious penetrating wounds and as a complication of pneumonia, it may be first serous and subsequently become purulent. It varies also in color and consistency, as well as in the variety and number of germs which it contains. A thick consistency naturally increases the difficulty of diagnosis by exploratory puncture. Purulent foci are also occasionally observed in the heart muscle. Thus, in the autopsy of Sibley's case, several small abscesses were found in the wall of the heart, and in another similar case, reported by Brentano, the direct cause of death was said to have been a rupture of such an abscess into the cavity of the left ventricle. In Sibley's case (Case XV), the pus had been detected by exploratory puncture, and although the heart proved to be deeply seated in the pericardium, a puncture of its wall by the exploratory needle is not inconceivable.

The lesions of pyo-pericarditis of unknown origin or of those due to penetrating wounds—the so-called primary cases—are not always confined to the pericardium and heart. The infection frequently spreads to the anterior mediastinum and contiguous pleura. In Coutts and Rowlands' case (Case VII), an autopsy, 16 weeks after the drainage of a pyo-pericarditis, complicating pneumonia and empyema, in a child two and one-half years old, showed that the entire anterior mediastinum was occupied by a thick, fibro-gelatinous deposit. In the writer's case, the anterior mediastinum was evidently infiltrated with a large serous exudate, the anterior wall of the pericardium lying at least an inch beneath the sternum. Such a condition may readily prevent the approximation of the divided edges of the pericardium to the skin, as recommended by Brentano, Porter and others, and necessitates the drainage of the abscess cavity from a considerable depth through the intervening mediastinum.

The changes in the pleura may either precede or follow those of the pericarditis. In the former instance a localized empyema associated with an infectious pneumonia, or merely the result of the lodgment of an infectious embolus, may invade either pleural cavity at a point remote from the pericardium. In the latter instance, the opposed surfaces of the pleura may at first be glued together by fibrinous exudate for the purpose of self-protection against the extension of the pericardial abscess. Such a barrier may subsequently prove inefficient, and a localized empyema close to the pericardium may appear, without, however, any demonstrable connection between the two abscess cavities. The importance of recognizing an associated empyema, whether primary or secondary, cannot be unduly emphasized, for in the event of such a complication it is only by proper incision and drainage of the purulent foci in both the pleura and pericardium that the recovery of the patient may be hoped for. The apposition of the opposed pleural surfaces by plastic exudate in the early stages of the extension of the pericarditic abscess may obliterate the corresponding part of the pleural cavity and may prevent a successful separation of the inner angle of the pleura from the anterior surface of the pericardium. Such artificial separation of the normal pleura is usually possible, and in pyo-pericarditis is always to be attempted by the surgeon in order that the underlying pericardium may be divided and the abscess material be evacuated without risk of pleural contamination.

Lesions in more remote parts of the body are those of the primary focus of infection, or of the resulting metastatic abscesses, and require no special description.

The clinical features of pyo-pericarditis form a distinct and typical picture only in the primary group of cases. Here the constitutional symptoms are those of a variable degree of sepsis, while the local symptoms are those of a pericarditis with effusion. On the other hand, in secondary pyo-pericarditis the symptoms are frequently masked by those of the primary lesion, and particularly in children the abscess in the pericardium may be entirely overlooked. In this group the diagnosis must be made chiefly on the character of the physical signs, although the chance of error is well shown by the testimony of several observers, who call attention to the similarity of the physical signs of fluid in the pericardium to those of a dilated heart. Although an exhaustive discussion of the differential diagnosis of these two conditions is beyond the scope of this paper, yet, as an important preliminary to exploratory puncture as a means of diagnosis, the writer wishes to emphasize the value of a differential leucocyte count. Coutts and Rowlands mention a "high" leucocyte count in a child one and two-thirds years old, and in the case reported by Scott the leucocytes, which, during a previous pneumonia were normal, increased in number as soon as the complicating pericarditis developed. In the writer's case a number of examinations of the blood gave an average leucocyte count of over 20,000.

In the presence of a high leucocyte count exploratory puncture is justifiable. The risks of this procedure have probably been overestimated. That the needle may enter the heart, and that this accident is favored by the intervention of the heart between the fluid and the chest wall, cannot be denied; that laceration of the heart may also be caused by contract with the pointed needle is also quite possible; and finally, equally true is it that the needle may penetrate the left pleural cavity with or without the lung, and so, in its withdrawal, form a new channel for the spread of the infection beyond the pericardium. In fact, such accidents are on record in medical literature. Thus Burtenshaw reports a case of paracentesis in which the trocar was first introduced into the right ventricle and ten ounces of blood were withdrawn before the mistake was discovered. This accident, however, did not prevent the patient's recovery. A. Meldon collected, in 1897, 100 cases of paracentesis of the pericardium with only one fatality from laceration of the right ventricle. Case XII, reported by Peters, seems to have been an instance in which a subsequent empyema may have been the result of infection spreading along the course of the needle from the punctured pericardium. On account of the rarity of these accidents, however, one should not be deterred from making the necessary exploration, especially when every preparation has been made for immediate operation in case pus is discovered, for with such a precaution the resultant damage to the heart, or the possibility of laying open new paths of infection along the course of the needle, would be greatly minimized.

The possibility of such accidents, however, has led to a wide variability in the choice of a site for puncture. The risk, theoretically, of penetrating the left pleural cavity, is shown by a study of the relation of its reflections to the chest wall. Investigations by Silk, Dwight and others, have shown that the median reflection of the left pleura lies under cover of the sternum at the fifth costal cartilage, and usually also beneath the sixth, while generally at the seventh there is an interval between it and the edge of the sternum. It is only, therefore, at or below this level that the pericardium can be entered in exploratory puncture without first passing through the overlapping pleura. This is probably the reason why Roberts and others favor a point of puncture close to the ensiform cartilage, opposite the seventh costal cartilage. That a similar condition would obtain in the presence of a pyo-pericarditis, might be inferred from the investigation of Delorme and Mignon, who have demonstrated the fact that distension of the pericardium with fluid has little or no effect in displacing the median pleural reflection outward. But artificial serous distension is not purulent distension, and according to the observation of Glück, the left lung, at least, is displaced so far outward, if not the pleura as well, that, in puncture made just within the outermost limit of the precordial dullness, the needle readily penetrates the distended pericardium without damage to the lung or its investing pleura. This view has the support of Curschmann and others, who unite in maintaining that exploratory puncture at the designated point is preferable, in that it incurs much less risk of tearing the heart, which is usually pressed forward, than a puncture close to the sternal edge.

In the writer's single experience, the left lung did not appear in the operative field, and the pleura was not opened in the exposure of the pericardium at a point one and one-half inches from the sternal edge, at the level of the fifth costal cartilage. Two preliminary exploratory punctures at a point slightly external had also proved harmless. That, on the other hand, the left pleural cavity has been opened in a number of operations for pyo-pericarditis, is a matter of record, and the occurrence of such an accident seems to depend upon the degree of plastic exudate, with consequent obliteration of the median pleural angle, which has taken place prior to the operation, and to which reference has already been made when speaking of the pathological changes of this condition. In general, it may be stated that, usually, sufficient obliteration has already taken place prior to the operation to minimize the danger of damage to, or contamination of, the left pleural cavity during the necessary exposure of the distended pericardium.

It is also important to emphasize that here, as in purulent collections of all kinds, exploratory puncture sometimes fails to withdraw pus. Thus Lyonnet reports a case in which two explorations proved unsuccessful, where, on subsequent autopsy, between fifty and sixty ounces of pus were found in the pericardium. In this case the heart, although adherent anteriorly, showed no trace of needle puncture. In every case of suspected pyo-pericarditis, where puncture is unsuccessful, the question of operative interference must be determined by the character of the physical signs, the degree of dyspnœa, the other symptoms of impeded and insufficient heart action, and the degree of leucocytosis.

In the consideration of the clinical features of pyo-pericarditis, mention has been made of a group of cases occurring especially in children, in which the lesion is overlooked. In this connection, it is well to call attention to the possibility of the local symptoms of this condition simulating those of a peritonitis. As in pneumonia, so in a pericarditis, and again especially in children, such a typical clinical picture is apt to occur, and even lead to the needless exploration of the abdominal cavity before the actual condition is recognized.

TREATMENT.

Except where the patient is already *in extremis* or moribund, operative treatment is indicated, and should take place without delay in all cases of suppurative pericarditis as soon as the diagnosis is confirmed by the needle. Moreover, in those cases in which exploratory puncture fails to withdraw pus, operation is justified by evidence of continued insufficient cardiac or respiratory action. Operative relief should also be extended to patients with advanced serous pericarditis in which aspiration either fails or is followed by rapid reaccumulation of the fluid with a return of cyanosis, dyspnœa, syncope or other serious symptoms.

Puncture, alone, in pyo-pericarditis, with the exception of a few scattered instances in which a cure has resulted from the gradual enlargement of the puncture channel into a permanent fistular, affords, at the best, but temporary relief. As a rule, the removal of pus in this way is but partial and its reaccumulation is rapid. Repeated punctures, in the hope of effecting a permanent cure, prolong the length of septic absorption and diminish the chance of success by subsequent operation. Its use, therefore, should be strictly restricted to diagnostic purposes.

Operation proper consists merely in the opening of the pericardium and in the provision for satisfactory drainage. For this purpose different routes have been either suggested or practised by their authors with the common object of minimizing the risk of opening the left pleural cavity. Thus Bacon advocates trephining the lower end of the sternum, but although, according to Curschmann, Riolan, Skelderop and Velpeau advocated a similar measure, no cases operated on by this route have as yet been reported. The writer suggests that the necessarily restricted space might unduly hamper the exposure of the pericardium, especially in the presence of an anterior mediastinitis, and would greatly increase the difficulty of suturing the divided edges of the pericardium to the skin. Furthermore, the constant passage of purulent material over freshly denuded bone might result in protracted if not a serious ostitis.

In cases, hitherto published, including those of the Roberts and Porter series, the pericardium has been opened after the resection of an overlying costal cartilage. Roberts suggests that a musculo-cartilaginous flap, consisting of the median portions of the fourth, fifth, and sixth costal cartilages and of the tissues of the intervening spaces, be raised from the anterior surface of the pericardium and pleura. This affords sufficient space for possible ligation of the internal mammary vessels, as well as for the outward reflection by the surgeon of the left pleural angle, thus avoiding the risk of opening that cavity in the subsequent division of the pericardium. After the evacuation of the pus, the flap is replaced, leaving a sufficient orifice for drainage. Roberts had no case to report and no instance of his operation has thus far been published. Although it gives admirable exposure and amply fulfills the objects for which it was devised, yet the very serious condition of many of these patients, especially in secondary cases, seems to demand an operation that combines the elements of speed and simplicity, such as may be obtained by the rapid removal of a single costal cartilage, rather than one which would necessarily severely tax both the resistance and the reparative power of the patient. Allingham has suggested a different route, the "epigastric," and has had several opportunities of testing its efficiency. In this operation, an incision made to the left of the median line just below the costal insertion of the rectus muscle, is gradually deepened upward through the costoxiphoid space in the diaphragm to the base of the pericardium, the peritoneum being pushed downward. It is thus seen to be a modification of Larrey's suggestion. In a discussion with Coutts and Rowlands, Allingham refers to three successful cases operated on by this method, the details of which, he declared, were to be published shortly. The operation certainly combines the advantages of opening the abscess in a dependent point and of probably avoiding the left pleural cavity. Its chief disadvantage is its length, the duration of the average operation being at least twenty minutes. The dangers of opening the peritoneal cavity and of hemorrhage from the terminal branches of the internal mammary artery are largely theoretical.

The simplest and most rapid exposure of the pericardium is accomplished by the removal of the inner part of either the fifth or sixth costal cartilage, through an oblique incision parallel to its long axis. This opening is deepened into the anterior mediastinum by the division of the perichondrium and the underlying plane of the tringularis sterni. The condition of the contiguous pleural reflection is then, if possible, determined. In the absence of adhesions the pleural angle is pushed outward without, if possible, any extension of the external incision. If obliteration of the pleural cavity has taken place, the underlying pericardium may readily be opened without danger of pleural penetration. The presenting pericardium is best divided by scissors between two pairs of forceps and the opening sufficiently enlarged to permit the passage of a finger. The pus is allowed to escape slowly in order that the heart action may not be unfavorably influenced. As the flow of pus ceases, the finger may be cautiously introduced through the opening and passed backward to either side of the heart with the object of separating adhesions as well as of detecting any hidden accumulation of pus that may have become shut off from the main cavity.

Usually subsequent irrigation with either a saline or weak antiseptic solution is desirable, if adequate provision is made for the free exit of the fluid from the interior of the pericardium. Failure to observe this precaution probably determined a fatal issue in Parker's case (cited by Roberts). The irrigation may be omitted if the patient's condition demands a speedy termination of the operation. No irrigation was used in the writer's case.

The divided edges of the pericardium should now be sewn to the skin wherever that is possible. This not only facilitates drainage but diminishes the risk of contamination of the anterior mediastinum. Such approximation may be prevented by a deep seated pericardium or, as in the writers' case, by a pre-existing mediastinitis.

Drainage is undoubtedly favored by the movement of the heart, which, in the absence of adhesions, tends to force out any accumulated pus, even though the opening is not at the lowest point of the pericardiac sac. It is still further assisted by the insertion of either a rubber drain or a capillary drain of gauze, into the abscess cavity, care being taken that they are so introduced as not to interfere with the action of the heart. Riedel (*Zentral. fur Chir.*, 1897, p. 56) states that, in one of his cases, the use of a rubber drain caused stormy and irregular heart action and had to be discontinued. In the writer's case a rubber drain and, after several weeks, a drain of gauze, was used without any indication of cardiac interference. As the discharge decreases the drain should be shortened and its use discontinued at the earliest possible moment. The persistence of a sinus rarely occurs.

After healing is complete, insufficient or irregular heart action is the marked exception; neither is there any indication of cardiac displacement. The patient, whose case is here reported, was in excellent condition after more than two years had elapsed since the operation, the precordial scar being the sole evidence of the former trouble. In the interval she has passed through one uneventful pregnancy.

That such a satisfactory result cannot always be expected, however, is shown in the report of a case by J. A. Scott, in which, four months after an operation by LeConte, for a pyo-pericarditis complicating pneumonia, in an adult of thirty-six, palpitation sufficient to interfere with the patient's work was present, although there was no physical sign that would indicate an adhesive pericarditis.

In conclusion, the belief cannot be too strongly emphasized that every case of pyo-pericarditis in which the patient is not moribund, should be treated by an operation which, in those cases in which a general anæsthetic cannot be tolerated, may yet be successfully carried out under cocaine or some other suitable local anæsthetic.

Brief abstracts of cases published since 1900 follow:

CASES GATHERED FROM LITERATURE.

1. (Reichard, Zentral. fur Chir., 1900, p. 1,109). Sex and age of patient not given. Pericarditis the result of penetrating stab wound with a knife. Oper-

ation by Lindner. Because of the almost moribund condition of the patient, the almost imperceptible pulse and great dyspnœa, was done largely without an anæsthetic. (Anæsthetic not mentioned). The pericardium was exposed by resection of the third costal cartilage and the ligation of the internal mammary artery, the abscess cavity being incised without damage to the pleura. There was a large amount of foul pus. Two thick drains with tampnoade of wound. The operation, which lasted ten minutes, was followed by a gradual improvement of both pulse and respiration. Complete recovery at the end of six weeks.

2. (*Ibid*). Etiology; influenza and rheumatism. The diagnosis was confirmed by puncture in the fifth left intercostal space outside the nipple line, a quantity of sero-hemorrhagic exudate being withdrawn with abundant pus cells. The condition of the patient was such as to forbid the extended use of a general anæsthetic.

Operation consisted in the resection of the fourth costal cartilage, the pleura being pushed to one side. On opening the pericardium a large amount of clear fluid forcibly projected. On account of the stormy action of the heart no drain could be inserted into the abscess cavity. A drain, however, was placed down to the pericardium after the suture of its edges to the muscle wall. The recovery was gradual and was marked by a somewhat irritable heart action.

During the ensuing discusssion Lindner stated that the selection of a different costal cartilage in these two cases was due to the difference in the extent and degree of the precordial dullness.

3. (W. Mintz, Zentral. fur Chir., 1904, 31, 59-61). History, cause, etc., not given. Operation under cocaine anæsthesia; the fifth costal cartilage was exposed and resected through an incision over its long axis. On account of the fact that the opening did not correspond to the most dependent part of the pericardium, a second incision was made along the lower border of the seventh costal cartilage and the pericardium exposed by blunt dissection. During convalescence almost the entire discharge passed through the lower opening. The statement is also made that this route was followed on one occasion by Larrey and that there is no danger of wounding the peritoneum if the exposed diaphragm is pushed downward and the pericardium entered at the inner angle of the incision.

4, 5, and 6. Mentioned briefly by Allingham as three successful cases, of which the details were to be published shortly, in the discussion with Coutts and Rowlands.

7. (Coutts and Rowlands, Brit. Med. Jour., 1904, 1, 9-13). Child, two and one-half years. One month prior to admission to the hospital the patient had had pneumonia with an incomplete recovery and with some loss of flesh.

Physical examination revealed a condition of rickets. There was an increase in the area of cardiac dullness and an almost imperceptible apex beat. The heart sounds were weak but pure. There was no friction sound. The pulse was 136, regular and of fair tension. On the right side posteriorly there was dullness from the sixth rib downward, passing around the axilla towards the front of the chest. Over this area there was faint bronchial breathing. The left lung was normal. The respiration was 58, and the temperature varied between from 99° to 104° in the afternoon. Exploratory puncture yielded nothing but a little blood. During the next five days the precordial dullness gradually extended upward. The apex beat disappeared and the pulse, still regular, became more rapid and feeble.

Operation by Rowlands under chloroform. The pericardium was exposed by resection of the fifth left costal cartilage, the adjacent pleura being displaced outward. A half pint of pus, rising to the height of three feet, issued from the interior of the pericardium. Insertion of the finger into the abscess cavity. Large rubber drain. No irrigation. The immediate effect of the operation on both heart and respiration was beneficial.

On the following day, exploration of the right pleura yielded pus and, under chloroform, resection of rib in the posterior axillary line with incision of the underlying pleura. For three days thereafter the condition of the patient was variable, although on the whole improved. On the fourth day after the original operation, the patient developed measles, with a subsequent pneumonia, death taking place at the sixth week from inanition, there having been a free discharge from the pericardium to the end.

Autopsy. This showed the entire anterior mediastinum occupied by a thick gelatinous deposit. In attempting to separate the pericardium from the left pleura an abscess cavity was opened, being a part of the pericardium behind and to the left of the heart.

In the discussion Rowlands stated that it was impossible to open the pericardium behind without damage to the adjacent pleura, the larger azygos vein and the thoracic duct.

8. (Coutts and Rowlands, Brit. Med. Jour., 1904, January 22). Male. One and two-thirds years. Family history of phthisis. Measles, 8 weeks before admission. Ever since a cough, increasing in intensity, has persisted. There has been much sweating. Patient complains of pain in the abdomen and loss of appetite.

Physical Examination. The general condition is rachitic, and wasted. There are signs of consolidation over the right chest posteriorly, extending around into the axilla as far as the mammary line. The apex beat of the heart lies in the fourth space just within the nipple. The sounds are clear and distinct. Left lung is normal. At no time is the temperature higher than 100° and exploration of the chest fails to detect pus.

On the ninth day after admission, a patch of dullness appeared over the left base posteriorly and a needle inserted withdrew clear serum. The temperature became irregular.

On the 21st day precordial dullness was first noticed. At the end of a week it had extended upward to the first rib and over to the right of the sternum. Heart sounds were inaudible below the third space and very feeble above that line. The pulse was very rapid and almost imperceptible. Leucocytosis 32,000.

Operation. Chloroform. Although puncture at the point indicated by Roberts, as well as in the fifth left intercostal space, failed to withdraw pus, the pericardium was exposed through the resection of the seventh costal cartilage and the adjacent part of the gladiolus. On opening the pericardium, between one and two ounces of pus escaped. The finger was passed to the base of the heart and into the oblique sinus below the heart. Drainage with two soft rubber tubes.

Patient gradually sank and died on the second day.

Autopsy. The lesions pointed to a long existence of a pericarditis. Culture from the pus yielded pneumococcus. A thick layer of gelatinous pus covered the opposed parietal and visceral layers of the pericardium.

9. (Kiliani, Annals of Surgery, 1907, 45, p. 130). Male; aged twenty-two years. Admitted to the German Hospital in 1901 for an attack of acute articular rheumatism, complicated by endocarditis and pericarditis. The pericardial effusion rapidly increased and became so threatening as to require immediate incision. Drainage of the pericardium was continued for seven days, after which time all oozing ceased. Immediately after incision, the patient, who had been moribund, showed signs of improvement, and his further recovery was uneventful. Five years after the operation the patient was in excellent health.

10. (Gengenbach, Colo. Med., Denver, 1906, 3, 187-190). Male; aged eight years. Mumps three years ago. Measles twice two years ago with an interval of six months between attacks. Scarlet fever complicated by mastoid suppuration ten months ago. For the past six weeks has suffered from whooping cough and while the cough still persisted, the present illness began, three weeks before admission to the hospital, with headache, vomiting, abdominal pain and some fever. Pulse of 120 and respiration of 40. Although there was no local tenderness or rigidity a diagnosis of appendicitis was made. The chest showed the physical signs of either a broncho-pneumonia or a pericardial effusion.

Two days after admission patient became deeply cyanosed with syncope. At that time the apex beat was not visible, but was faintly palpable about one inch within and to the level of the nipple. The heart sounds were audible but indistinct. Cardiac dullness extended from the second to the sixth rib and from one inch to the right of the sternum to the left mammary line. Paracentesis.

Two days after paracentesis, operation under chloroform by Dr. Craig. The fifth rib, one and one-half inches to the left of the sternum was resected, the pericardium opened and one and one-half pints of pus evacuated. Rubber drain. Free discharge. "Double" coccus found in pus. The patient collapsed by operation, rallied. Although the discharge gradually lessened and the tube could be withdrawn three days before the patient died, a fatal issue could not be averted.

Autopsy. There was a large abscess occupying the entire left pleural cavity. There was no communication between this cavity and that of the pericardium.

11. (J. A. Scott, N. Y. Med. Jour., 1904, 1, 198-200). Male laborer; aged thirty-six years. Patient gave a history of pneumonia of the right base of six days' standing, which, on the third day, spread to the left base with pleurisy.

On the thirteenth day the apex beat was neither visible or palpable. There was no pericardial friction. On the eighteenth day the patient developed a pulsus paradoxus and exploration in the fourth right space withdrew serum which obtained the pneumococcus. On the following day, exploration in the same place withdrew fourteen ounces of sero-turbid fluid. Seven days after the needle withdrew thick yellow pus. (With the advent of the pericarditis, leucocytosis, which, during the pneumonia, had been normal, materially increased).

Operation under chloroform by LeConte. On account of cardiac weakness the chloroform was superseded by cocaine. Through an incision in the fifth space the pericardium was opened and between a pint and a quart of pus evacuated. Rubber drain, which was removed on the twenty-sixth day after operation. Four months after operation palpitation still persisted and prevented the patient's working.

12. (G. A. Peters, Edinb. Med. Jour., 1903, n. s. 13, 209-216). Male; aged seven years. Patient had both measles and scarlet fever some years ago. One month ago, preceded by malaise of three days' duration, patient developed severe pain and tenderness about the umbilicus. The pulse increased to 100, the temperature to 100°-102° and the respiration was short, frequent aud grunting. The abdomen gradually became prominent and purgatives and enemata failed to act properly. In the second week of his illness the tenderness became limited to the upper part of the abdomen and dullness was elicited above the level of the umbilicus. Soon after dullness appeared over the left side of the chest, with diminished respiratory murmur. Dyspnœa appeared and increased in severity. It was urgent at the time of admission.

Physical Examination: The respiration was thoracic. There was dullness over the left side, especially anteriorly. The cardiac impulse could not be detected. Anteriorly the dullness extended up to the clavicle; posteriorly to the spine of the scapula, extending beyond the sternum to the right nipple and merging with the liver dullness below (a marked example of Rotch's sign of fluid in the pericardium). On auscultation the heart sounds were fairly audible about the left nipple with a slight systolic murmur. There was tubular breathing over the left chest. The fluid which was withdrawn from the pericardium by three widely separated punctures was opaque and rich in cellular elements.

Operation: An incomplete operation was done through the fourth space three-quarters of an inch to the left of the sternum and ten ounces of fluid withdrawn. The rubber drain was soon blocked with lymph and became ineffective. The urgency of the symptoms was much relieved. During the two days following, however, the patient became steadily worse with cyanosis and subnormal temperature, at the end of which time a complete operation was done under local anæsthesia, as follows:

An incision was first made in the fifth space one-half inch to the right of the sternum and abandoned on account of the exposure of the pleura. An incision was then made in the fifth space on the left side and the pleura opened and packed without reaching the abscess cavity. The pericardium was then successfully exposed through an incision in the left fourth space, three-quarters of an inch from the sternum, and twenty-nine ounces of pus containing the staphylococcus aureus evacuated. Drainage with a long rubber tube. The discharge of the pus was followed by a return of the liver to its normal position.

Two weeks after this operation the dyspnœa increased and the general condition became weaker. Exploratory puncture at the angle of the left scapula withdrew pus, and under ether, thirty ounces of that fluid was evacuated from the left pleural cavity without the resection of a rib.

The patient eventually recovered and eleven months after the operation could play around as well as ever.

13. (Arthur Latham and H. S. Pendlebury, Lancet, 1903, 1, p. 798). Male; aged fifty-three years. Six months before admission became short of breath which, five months later, compelled him to give up work. At this time the left pleural cavity was tapped and ten ounces of serum withdrawn. The tapping was repeated on four different occasions afterward. Two months ago œdema of the legs, with some distension of the abdomen, appeared. There was jaundice.

On admission the patient complained of sleeplessness and of cold extremities. The patient also complained of a cough, with expectoration, and of considerable shortness of breath with cyanosis. The pulse was 74, respiration 24, and the temperature was normal.

Physical Examination: The cardiac apex could neither be seen, felt nor heard. The precordial dullness was much increased. There was dullness, diminished voice sounds and tubular breathing over the left axillary base. Over the left base posteriorly, the percussion note was impaired, the breathing distant and tubular and there were a few moist sounds. There was œdema of both lower extremities and the physical signs of ascites. Tapping two days after admission in the fourth space one and one-quarter inches to the left of the sternum, withdrew ninety-five ounces of serous fluid of a brown color from the methæmoglobin which it contained. This was followed by a decrease in the œdema and in the abdominal distension. The cardiac sounds, although faint, were nevertheless distinctly audible, Owing to a recurrence of the fluid and its associated symptoms, operation under chloroform by Pendlebury one week after the aspiration.

An Allingham operation was done and additional exposure gained by resection of the sternal end of the sixth costal cartilage. The finger inserted into the pericardium. There were no adhesions and the surface of the heart was smooth. One edge of the pericardium was stitched to the lower corner of the wound, a tube having been inserted into its cavity. The tube was removed on the fourth day and healing was complete at the end of the fourth week. At that time the patient was entirely free from dyspnœa, ascites and œdema. He also slept well at night. Four months after the operation patient returned to work.

14. (A. Hall, Lancet, 1908, 2, p. 951). Female; aged thirty-eight years. One month prior to admission patient was confined. One week later advent of puerperal sepsis with double pneumonia. The abdominal symptoms disappeared but the fever and weakness continued and on admission patient complained of extreme dyspnœa and had the appearance of being very sick.

Physical Examination: The left side of the chest was almost motionless. No cardiac impulse palpable. Area of cardiac dullness extended from the upper border of the second left rib above, one-half inch to the right of the sternum. On the right side laterally it extended down as far as the fifth rib and on the left side it corresponded to the mid-axillary line. The heart sounds were almost inaudible over the entire area.

There was a slight pleuritic friction sound in the fifth space near the nipple. There was dullness at the right base and moist sounds over both bases posteriorly. The abdomen was full and distended but without sign of fluid. Urine scanty but normal. The pulse was 132, respiration 60, and the temperature between 100° and 101°. There was a slight but frequent cough. A needle passed into the fifth space passed through the diaphragm, which is near the edge of the sternum, and at the level of the nipple. In the fourth space it passed into the pericardium and withdrew pure pus.

Operation by Wilkinson. Chloroform. Excision of the fourth left costal cartilage; twenty ounces of grey-yellow pus were evacuated without damage to the pleura. The pericardium was sutured to the skin and a large soft collapsible tube inserted. A profuse discharge continued to the death of the patient, one week after the operation.

Autopsy. There was a small purulent pleuritic effusion over the right base. The death of the patient seemed to have been the result of a general suppurative peritonitis, with dilatation of the stomach, which accounted for the unusually high position of the diaphragm. Examination of the pus in the peritoneal cavity showed both staphylococcus and streptococcus.

15. (W. K. Sibley, Brit. Med. Journal, 1903, 1, 1192). Male; aged sixteen years. Prior history negative. Sudden onset of tonsillitis, followed in three days by pneumonia. This ran a severe course, the pulse rising to 150, the respiration to 50–60, the temperature to 103° on the sixth day. At that time there were pleuritic râles outside the left nipple and impaired percussion over the left base. One week after the invasion of the tonsillitis there was pain with fullness and tenderness in the epigastric region. The heart sounds were indistinct, but there was no bruit. On the ninth day resolution by crisis occurred, with rapid disappearance of all pulmonary symptoms. On the other hand, the area of cardiac dullness increased and the apex beat could not be felt and the heart sounds became very faint. In this condition the patient remained until the twenty-first day of the illness. On that day he became cyanosed with much dyspnœa, especially while supine. The cardiac dullness increased both in an upward and outward direction. There was pulsus paradoxus, and on the following day the patient became pulseless. The heart sounds were scarcely audible. Pus was withdrawn by exploratory puncture in the area of precordial dullness and was found to contain the pneumococcus.

A. C. E. mixture, afterward replaced by ether.

Operation by Lane. Under a general anæsthetic a local empyemic abscess was exposed; after the resection of a portion of the sixth rib outside the nipple line the pericardium could not be felt.

Although somewhat relieved, symptoms indicating pent-up pus continued, and ten days later a search of the empyemic cavity disclosed the pericardium bulging into it in such a way that it could easily be reached and opened with the finger, ten ounces of pus similar to that originally found in the pleural cavity being evacuated. The heart was felt in the back part of the pericardium. A rubber drain at first inserted had to be discontinued on account of irritating the heart action. The pus was similar to that originally found in the pleural cavity. After a temporary improvement the patient continued to lose ground and died ten days after the last operation. The necessary withdrawal of the drainage tube seemed to interfere with the proper drainage of the abscess cavity.

Autopsy. There were a number of small abscesses in the wall of the heart from which some bleeding had occurred into both the pleural and pericardiac cavities. Pneumococci were found in great numbers in the blood. The writer states that probably a small amount of pus was present in the pericardium at the time of the first operation.

16. (Gluck, Verhandlung. d. deut, Gesell. f. Chir, 1907, 36, 378–385). Male; aged nine years. Extensive physical signs of fluid. Green-yellow pus withdrawn by needle in the fourth left space one cm. external to the mammary line. Sub-periosteal resection of the fifth rib from a point opposite the mammary line, four cm. externally. The pericardium was opened without damage to the pleura. At first the progress was satisfactory, but ultimately the patient died from general streptococcus infection. (See following case for a more detailed account of the operation and additional symptoms).

17. (Gluck, *Ibid*). Male; aged fifty-six years. Patient operated on in the above manner and three months after was completely well.

In cases 16 and 17 the patient had a pericardial reflex cough, difficulty in swallowing and a congested, enlarged liver (marked by peculiar intense pain and swelling in the left lobe of the liver). In case 16 this condition led to a primary laparotomy. In spite of an extensive exudate a pericardial friction sound was present in both cases.

The pericardium was exposed by a skin muscle flap, with its base in the mammary line, opposite the fourth, fifth and sixth ribs, and the fifth rib, for a distance of three cm. external to the mammary line, resected without damage to the pleura. In opening the pericardium the left border of the heart protruded, filling the opening so completely that only by the insertion of the finger between the heart and the inner surface of the pericardium could the fluid be evacuated. Drainage was continued for six weeks.

Before the operation the pulse was very irregular and over 150. Digitalis and morphine given, both before and after operation. Drainage somewhat interfered with by the forward protrusion of the heart.

18. (Steward and A. E. Garrod, Proc. Roy. Soc. Med, London, 1907, 1, 15–17). Female; aged five years. Two days prior to admission to hospital a tonsillectomy was followed on the same evening by pain in the abdomen and left chest. On admission the temperature was 103° and the pulse 120.

Physical examination showed the presence of fluid in the left chest below the angle of the scapula. One week later pus was withdrawn and a localized empyema opened and drained by the resection of a rib. The pus contained pneumococcus. The operation was followed by improvement but the temperature remained between normal and 102°.

Three weeks after operation. During the past few days the temperature has increased to 104°, the pulse to 140–150, the leucocytosis from 31,000 to 41,000 in an interval of two days. There have been two attacks of vomiting. Exploration of the old abscess cavity showed a bulging mass in the position of the pericardium. The child continued to grow worse, and three days later the cardiac dullness was found to extend two inches to the right of the sternum, and a skiagram showed a distinct shadow of a distended pericardium.

Operation. Under light anæsthesia the pericardium was opened through the empyemic cavity and several ounces of thick yellow pus evacuated. Drainage with a rubber tube.

After the operation the child's temperature gradually fell and reached normal in three weeks. Very little pus was discharged after the first day. Five weeks after the operation the wound had completely closed.

Four months afterward the child had recovered its normal weight and appeared to be in robust health. The pulse was 100 and regular. The lung had fully expanded.

19. (Godlee; discussion of above). The pyo-pericarditis was a complication of an acute infectious osteomyelitis and was operated on by Raymond Johnson through an anterior incision. Although the case was further complicated by abscess of the elbow, and later of the brain, the boy ultimately recovered. One year later the patient died of a recurrence of the brain abscess.

Although, because of the absence of details, no tabulation of the cases to which he refers can be made, it is interesting to note the statement of Samuel West in the same discussion, viz.: Dr. Samuel West had seen several similar cases in which the pericardium was opened from the back and the drainage secured was satisfactory. The majority of the patients had died because the pericarditis was of pyemic origin. In his experience the prognosis in pericarditis, the result of pneumococcus infection, was more favorable than in those due to streptococcus. One case was opened anteriorly with perfect drainage and the patient was practically well in a week. Another case similar to the one under discussion terminated in the death of the patient. The speaker thought that, ordinarily, simple incision anteriorly, without the resection of a rib, would provide satisfactory drainage.

20. (H. S. Pendlebury, Lancet, 1904, 2, 1145). Male; aged thirty-one years. Pneumonia in the left lung. Three weeks after invasion of pneumonia, the temperature remaining high, considerable cyanosis and dyspnœa developed and examination showed that the cardiac dullness extended four inches to the right of the sternum. The heart sounds were muffled. The pericardium was exposed by resection of the sixth and seventh costal cartilages, and between three and four ounces of serum evacuated. Adhesions between the heart and pericardium were broken down with the finger and a tube inserted. Rapid recovery, the tube being removed on the sixth day.

21. (*Ibid.*). Male; aged twelve years. On admission the patient was cyanotic and dyspnœic and presented the physical signs of serous pericarditis and of endocarditis, complicating an attack of acute articular rheumatism. Operation on the sixth day. The pericardium was exposed by resection of the seventh

costal cartilage only. In pushing aside the left pleura, the right pleura was accidently opened, but without appreciable harm to the patient. On opening the pericardium the fluid, which was under considerable pressure, rapidly escaped. Death occurred five days later, with little apparent benefit from the operation.

Autopsy. The right pleura projected beyond the left side of the sternum down to the level of the seventh costal cartilage. The opening in the pericardium was not recognized, both its visceral and parietal layers being in contact and adherent. There was much endocarditis with valvular varicosities.

Author's Case.

Presbyterian Hospital, April, 1906. N. N., female, aged nineteen years. Admitted to the service of Dr. J. S. Thacher and Dr. Bovaird. Patient has always been well. She was married eleven months ago and has been pregnant for the past two months. There is no discoverable cause of a primary focus of infection.

About six weeks before admission to the hospital, patient suffered from malaise. One week later pain in the left chest with cough appeared, the pain being intensified by a deep respiration as well as by the effort of coughing. At the end of another week dyspnœa developed, the symptoms already mentioned having increased in intensity. The bowels were loose, the patient having between fifteen and twenty loose, watery movements each day. These together with the other symptoms, caused general prostration. On admission to the medical ward of the hospital a physical examination showed a diffuse apex beat where the sounds of the heart were very indistinct. The area of cardiac dullness was enlarged to the right. There was a to-and-fro friction sound at the base. There was dullness with diminished voice and breathing from the angle of the scapula downward.

The patient ran an irregularly low temperature for several days. The left pleural cavity was punctured and three ounces of serous fluid withdrawn. About a week later after admission, premature labor occurred, with a normal breech presentation. Since then there has been an increase in the dyspnœa with intermittent fever. On the day before the patient was transferred to the surgical ward, puncture of the pericardium by Dr. H. H. Mason gave pus, containing streptococci. At this time, the chief complaints were the dyspenœa, the precordial distress and the intermittent temperature. Physical examination of the chest showed the left border of the precordial dullness to be eight and one-half inches to the left of the mid-sternal line, while the right border extended two inches to the right of the same line. The action of the heart was regular and varied between 110 and 120. The respiration was short, labored, between 40 and 50.

Two aspirations of the pericardium were made, the first of which, in the fifth space, one and three-quarter inches to the left of the sternum, was unsuccessful, although a little serum and a few flakes of fibrine escaped from the puncture orifice as the needle was withdrawn. The second aspiration in the left same space, two inches to the left of the midline, withdrew three ounces of thick yellow pus. Leucocytosis: March 15, 23,000. March 20, 31,200. March 24 (day after delivery), 24,600. March 26, 34,200. March 29, 18,800. April 1, 23,200.

Operation. Gas and ether. Dorsal position. Horizontal incision with resection of the fifth costal cartilage, one inch to the left of the sternum. The tissue of the anterior mediastinum was infiltrated and at least one inch in thickness and spongy. Along a needle previously inserted into the pericardium that cavity was opened with a bistoury and about one pint of pus allowed to escape slowly. The opening was still then further dilated with the finger, which could feel the heart beating distinctly. The pulse became quite rapid during the operation and for a short time after the pericardium was opened was irregular. There was considerable respiratory embarrassment. A rubber drainage tube was inserted and the angles of the incision sutured.

The patient responded well to stimulation with strychnine and whiskey and on the morning after the operation was in fair condition. The wound was dressed daily, both rubber and gauze drains being used. With the patient on a back rest, the dyspnœa was alleviated. In this condition the patient continued for a week, the abscess cavity draining freely and satisfactorily. One week after the operation, the temperature suddenly rose to 104°, the pulse to 140 and the respiration to 52. There was marked cyanosis, and the patient complained of dyspnœa and of precordial distress. Physical examination failed to disclose any explanation of these symptoms and on the following day they had subsided, the pulse decreasing to 120, respiration between 40 and 50, and the temperature to between normal and 101°. From this time further progress of convalescence was uneventful, the patient suffering from occasional slight dyspnœa only. The pulse continued to vary between 110 and 120 throughout. On May 3rd, patient was allowed in a chair, and on May 20th was allowed to walk. On May 11th, the rubber drain, previously shortened, was removed, and replaced by a small gauze drain which, in turn, was discontinued after the 25th of May. Two weeks later the sinus had entirely closed.

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VII.

PRIMARY CARCINOMA OF THE VERMIFORM APPENDIX.

A CRITICAL STUDY OF 90 CASES, WITH REFERENCES TO 123 CASES.*

By Clarence A. McWilliams, M.D.

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The increasing reports of isolated cases of primary carcinoma of the appendix, which one finds in the literature, testify not only to the greater interest now manifested in the study of the pathological anatomy of that organ, but also to the greater care exercised in its examination, whether removed at operation or on the autopsy table. A sufficient number of such neoplasms has now been recorded to make a critical study of them interesting and instructive. To the 87 cases that I have found reported in the literature, I desire to add the following 3 cases:

Case XXII.—An unmarried, German, immigrant girl, aged twenty years, was admitted, on September 5th, 1907, directly from the steamer to the Presbyterian Hospital, to the service of Dr. F. T. Brown, to whom I am indebted for the privilege of taking care of and reporting the case. Except for some seasickness, she had been well up to two days prior to landing, at which time she was taken with severe pain in the right side of the abdomen. She had fever, and was markedly prostrated. The right lower quadrant of the abdomen became very tender to pressure. On admission to the Hospital, her temperature was 101°, and her pulse

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* The reports of 33 additional cases were found after the statistics in this article had been completed. Since it was impossible to include them in the detailed study, they have been added in an appendix. The total number ot cases reported, therefore, is 123. The literature is brought down to Jan. 1, 1909.

100. The leucocytes were 23,000, and the polymorphonuclears, 88 per cent. She had never been sick before, and there was no history of any pelvic disturbances. While evincing evidences of considerable prostration, at the same time she was very well nourished, and there was no sign of any cachexia. Physical examination showed the heart and lungs to be normal. The abdomen was distended and there were no respiratory abdominal movements. The whole right lower quadrant was rigid and very tender, both these signs shading off from a point of maximum intensity, situated at McBurney's point, where there was felt a mass the size of a lemon. Over this mass there was tympany, and there were no signs of free fluid in the abdomen. Rectal examination showed the pelvic organs to be normal, and no mass could be felt, but there was considerable tenderness high up in the right fornix.

Immediate operation was performed. An intermuscular incision, about two inches long, was made over the mass. On opening the peritoneum, the inserted finger pushed aside an adherent coil of intestine, which opened an abscess, well walled in, containing about two ounces of fetid, thick, creamy pus. After sponging the cavity dry, the appendix was found hanging over the brim of the pelvis, to whose walls it was adherent. On delivering it into the wound, it was seen to be about four inches long and as large as one's index finger. Its serosa was intensely congested, and about one inch from its base there was a gangrenous patch, in the centre of which there was a small perforation. Its tip was clubbed and hard, as though there was a concretion in its lumen. The meso-appendix was clamped in sections and divided. Two catgut ligatures were applied about its base, between which the appendix was amputated. The stump was cauterized by the Paquelin, after which a second plain catgut ligature was applied about the stump, which was followed by a second cauterization. The cavity was sponged out, and into it were inserted two small cigarette drains. The abdominal wall was sutured by layers, closely about the drains. The patient made an uneventful recovery, the wound being completely closed by the twenty-fifth day. The girl went home on the thirtieth day.

At the time of the operation there was no suspicion that the appendix, on external examination, was affected with anything more than an intense, acute suppurative inflammation. Owing to the lateness of the hour in the evening of the operation, the appendix was not cut open, but, following the ordinary routine, it was sent, as it was removed, to the pathologist, by whom a gross section of the organ was made, and this revealed, macroscopically, that the tip, for half an inch, was occupied by a small fibrous appearing mass, which completely filled the lumen. There was no concretion present. No suspicion of malignancy whatsoever was aroused at the time of the operation, as there was no tumor visible on the external surface, the tip being merely clubbed. No enlarged glands were seen in the meso-appendix.

The following is the report of the examination of the specimen by Dr. F. C. Wood, of the Pathological Department of Columbia University: The material consists of four transverse sections of the appendix. Two of the fragments include a considerable portion of the meso-appendix. The other two are transverse sections of the free part of the organ. The appendix is considerably enlarged, measuring about 12 mm. in diameter after hardening. Two of the sections show merely a dilated appendix with no mucosa and a somewhat chronically inflamed peritoneum and subserous coats, the wall measuring 4 mm. in thickness. The other two specimens, which include the meso-appendix, show the following changes: The wall is thickened, measuring 6 mm. This thickening is chiefly in the submucosa and muscularis. At the periphery of the appendix and in the meso-appendix are a large number of leucocytes and blood. The leucocytes are chiefly polynuclear, many of them of the eosinophile group. The rest are lymphocytes and plasma cells. The fat of the meso-appendix is infiltrated, and there is a formation of a considerable amount of new connective tissue in the form of granulation tissue.

The blood vessels are distended with blood. There is a thrombus in one of the larger veins. This more or less active inflammation extends entirely around the appendix, although in the portion opposite the mesenteric attachment the inflammation is much less than on the other side. The mucous membrane of this portion of the appendix is normal and the surface is unbroken. The submucosa, the muscularis, and the subserosa are infiltrated with cells arranged in large and small masses in the tissue spaces (Figs. 1, 2, and 3). These cells are polyhedral (Figs. 4 and 5); there is no connective tissue between the individual cells; the nuclei are large and show well arranged chromatin network. Mitotic figures are scanty. None of the carcinomatous masses show any tendency to an alveolar formation, nor are there any high cylindrical or mucous cells. While the new growth extends up into the lymphoid tissue underneath the lining membrane of the lumen of the appendix, this epithelium is in no place broken through, nor in direct connection with the growth. The infiltrated tissue shows the usual evidence of chronic inflammation, and many wandering tissue cells of the type of plasmacytes and plasma cells are present in the muscle bundles near the new growth. The exact histogenesis of the tumor cannot be established from the specimen, as the entire appendix is not available for section; but the possibility of the tumor having arisen from the mucous membrane cannot be excluded. The diagnosis is carcinoma of the appendix, polyhedral cell type; acute peri-appendicitis.

Case XXVI.—Operator, Dr. J. Wiener. A male, aged thirty-five years, was admitted to Mt. Sinai Hospital, New York, December 8th, 1903. As a child, inflammation of bowels. Five years ago, indigestion for six months with nausea and belching of gas, appetite fair, but with no pain. One year ago, nervous prostration, which kept him from work for six months. Moderate smoker, but not alcoholic. Eleven days before admission, sudden sharp, shooting pains in right lower quadrant. Next morning

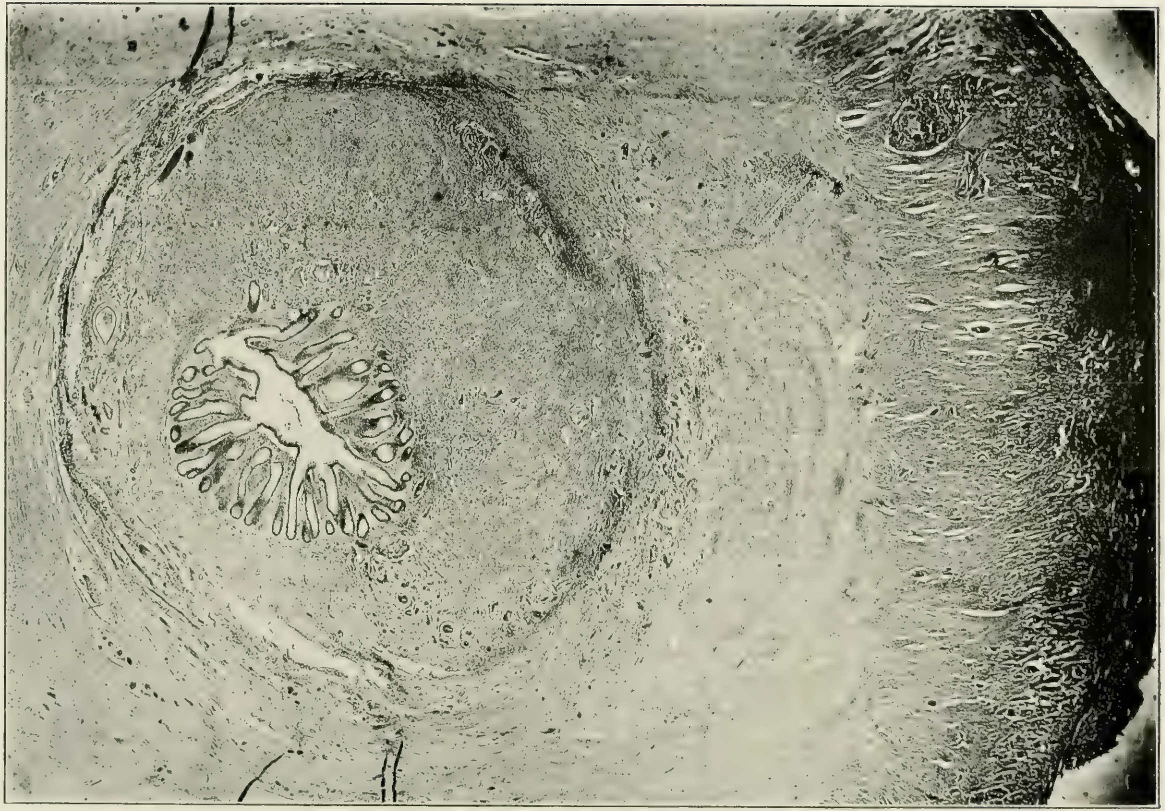

FIG. 1—CARCINOMA OF THE APPENDIX (CASE XXII)

SHOWING GENERAL DISTRIBUTION OF THE GROWTH THROUGHOUT THE WALL OF THE ORGAN. (LOW POWER.)

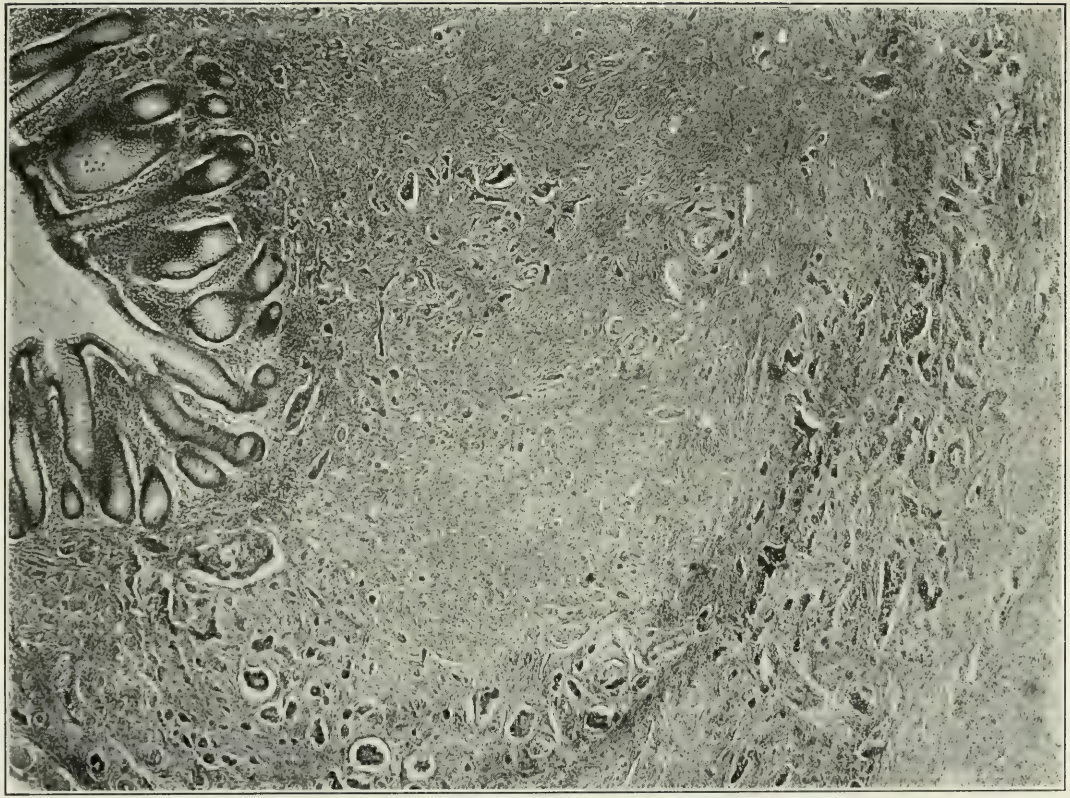

FIG. 2—CARCINOMA OF THE APPENDIX (CASE XXII)

SHOWING GENERAL DISTRIBUTION OF TUMOR THROUGHOUT THE WALL OF THE APPENDIX. (MEDIUM POWER.)

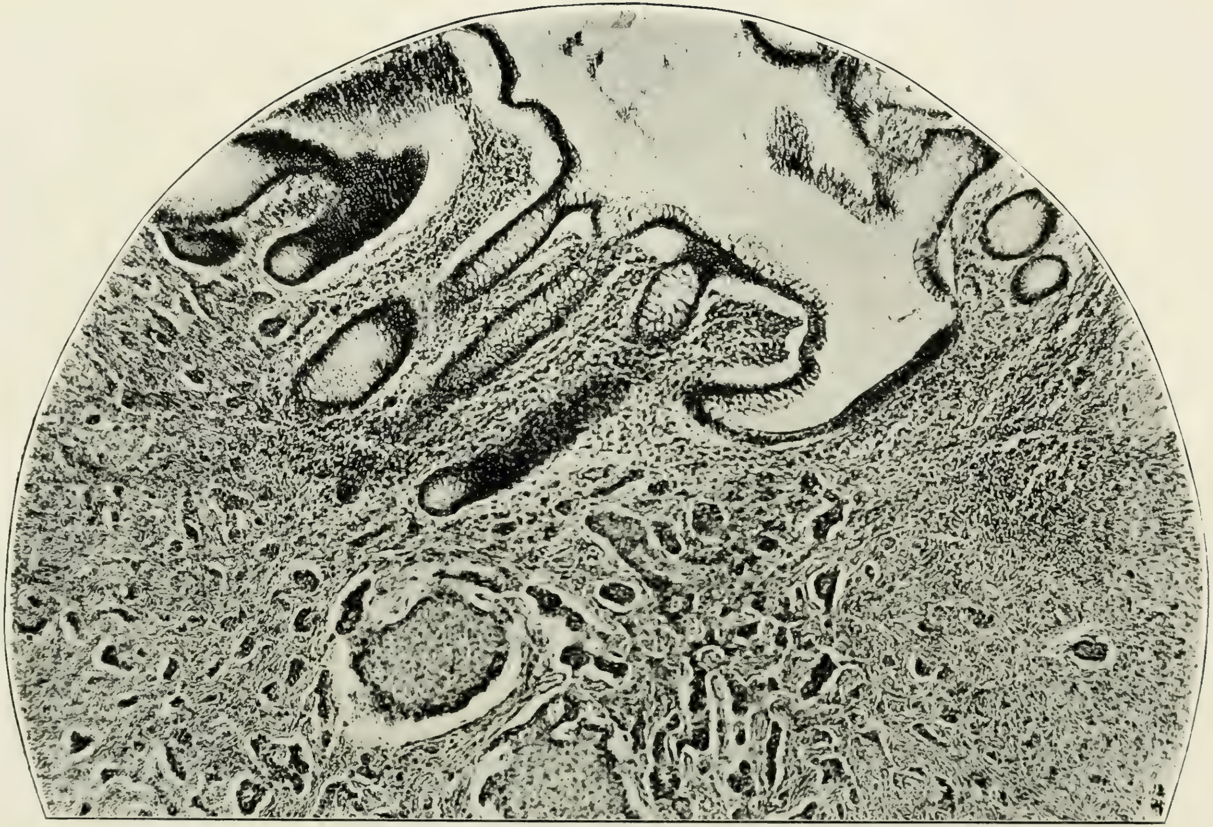

FIG. 3—CARCINOMA OF THE APPENDIX (CASE XXII)

SHOWING THE TOPOGRAPHY OF THE GROWTH BENEATH THE MUCOSA. (MEDIUM POWER.)

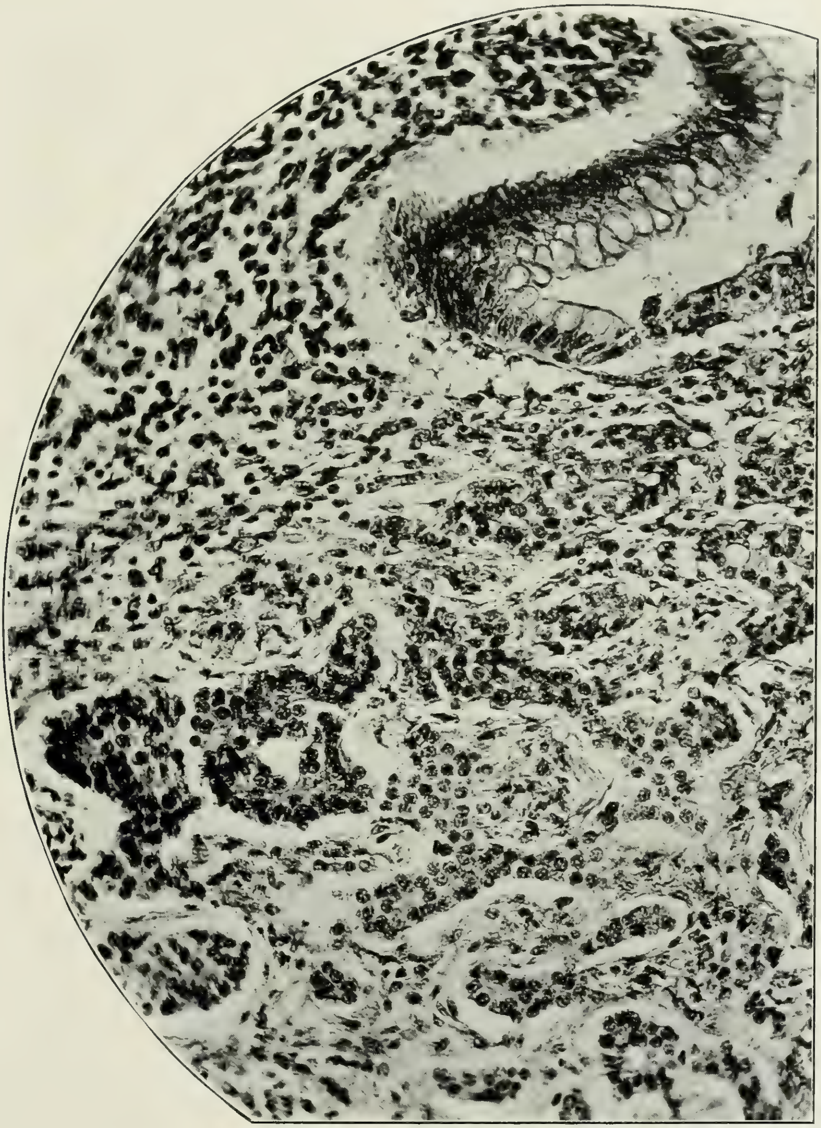

FIG. 4.—CARCINOMA OF THE APPENDIX (CASE XXII)

SHOWING SOLID ALVEOLI FILLED WITH POLYHEDRAL CELLS INVADING THE SUBMUCOSA. (HIGH POWER.)

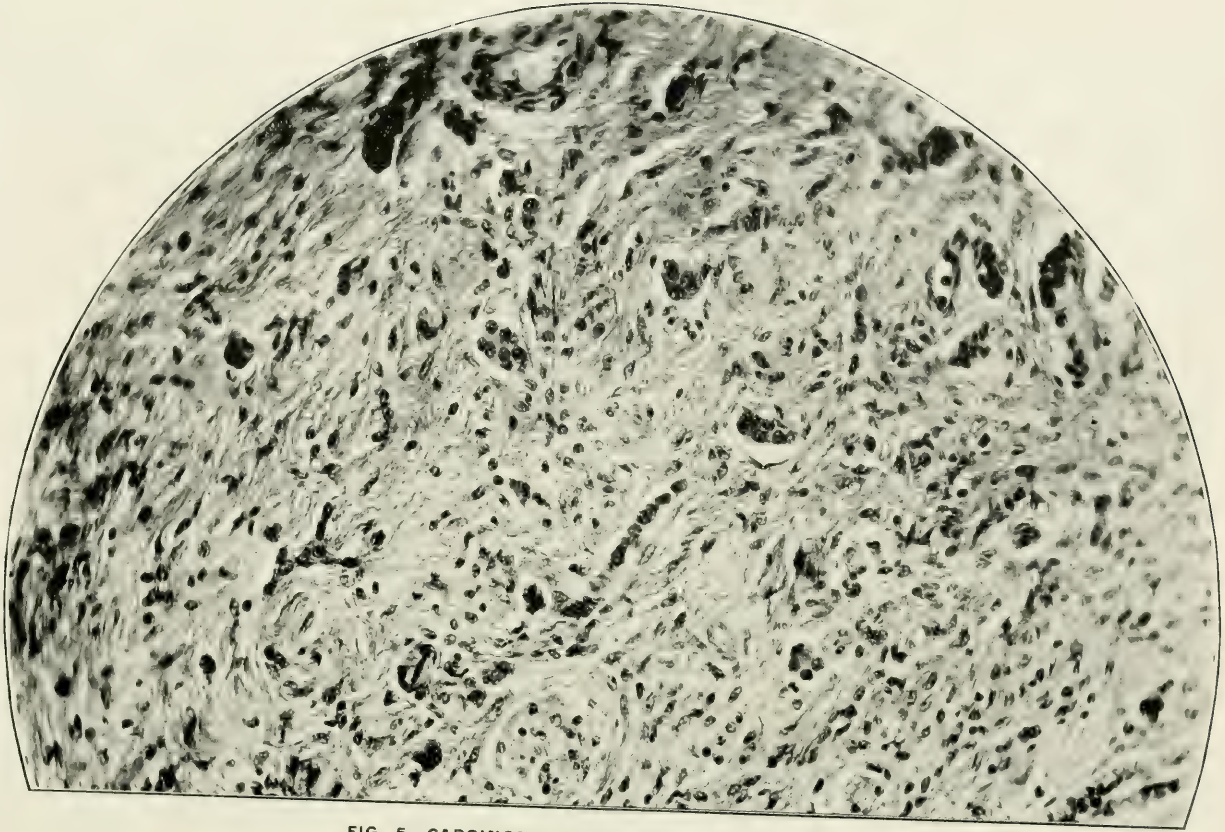

FIG. 5—CARCINOMA OF THE APPENDIX (CASE XXII)

SHOWING SOLID ALVEOLI FILLED WITH POLYHEDRAL CELLS (HIGH POWER)

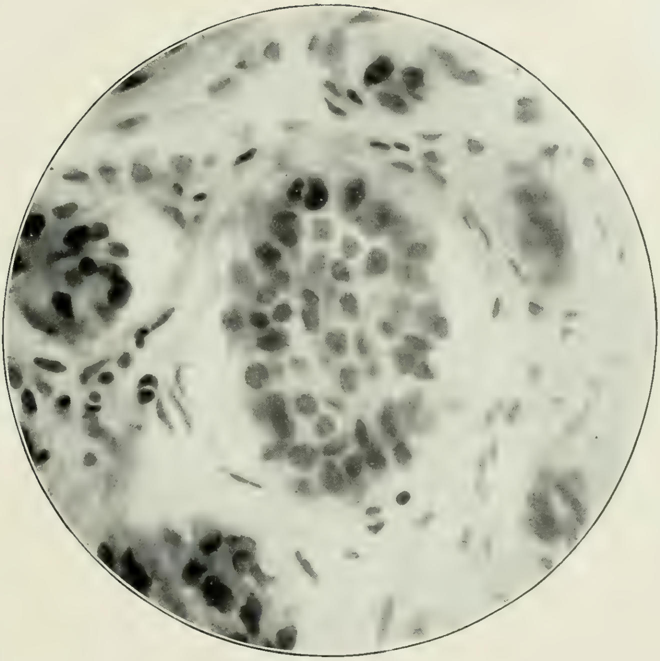

FIG. 6—SPHEROIDAL-CELL CARCINOMA OF THE APPENDIX (CASE XXVII)

SCATTERED IRREGULARLY BETWEEN THE MUSCLE BUNDLES ARE ALVEOLI FILLED WITH IRREGULAR OVOID OR POLYHEDRAL CELLS WITH LARGE NUCLEI. IN OTHER PORTIONS THERE IS A DIFFUSE INFILTRATION OF THE MUSCLE TISSUE WITH SIMILAR CELLS. THERE ARE NO MITOSES VISIBLE IN THE CELLS. DIAGNOSIS: SPHEROIDAL CELLED CARCINOMA OF THE APPENDIX.

went to business, but about 11 A. M. felt nauseated, with chilly sensations and profuse sweating. Severe umbilical pains. A few hours later, temperature 103.6°. No vomiting. Bowels moved spontaneously. Went to bed and had fever and chilly sensations for three days, when the pain became localized in the right iliac fossa. Operation December 9th, 1903, at which time nothing palpable in the right iliac fossa was felt, but there was slight tenderness on deep pressure in that region. Intermuscular incision. Many dense adhesions between cecum, parietal peritoneum, and ileum. Appendix firmly adherent below and internally to cecum. Separation of adhesions caused tearing of serosa of cecum in several places, which were repaired with silk sutures. Appendix two inches long, very narrow, especially at base; near its tip, and projecting into the meso-appendix, was what was taken to be a small gland. In the mesentery, near the ileocecal junction, a large gland was found and removed. This gland, together with the tip of the appendix, was submitted to the pathologist, Dr. Mandlebaum. Out of bed on the tenth day, and the wound healed in two weeks. The diagnosis is adenocarcinoma near tip of the appendix; obliterating appendicitis; hyperplasia of mesenteric gland. The patient was well four years later, that is, at the present time.

Case XXVII.—Operator, Dr. A. J. McCosh. A male, aged twenty-five years, was admitted to the Presbyterian Hospital, New York, April 7th, 1897. His difficulty began in the previous August, when he had sudden cramp-like pains in the right lower abdomen, accompanied by vomiting. No abdominal tenderness (?). The pains lasted two weeks. The next month, September, he had a similar attack, lasting three weeks. He was well until the following March (an interval of six months), when he was taken with sudden tenderness and pains in the right iliac fossa, abdominal distention, and vomiting. On admission, he was just recovering from this last attack. On examination, there were rigidity and tenderness in the right iliac fossa. At the operation there was no fluid in the abdomen. There was felt a mass, three and one-half inches in diameter and one and one-half inches deep, with no pulsation in it. It was gradually mapped out, running obliquely behind the posterior peritoneum from the sacrum up to the right side. The appendix was not seen. An aspirating needle introduced into the boggy tumor withdrew no pus. It was deemed a malignant mass, involving the cecum, appendix, and peritoneum. Removal was considered impossible, and the wound was closed. The patient was readmitted January 4th, 1899, twenty months after his first operation. For the past eight months he has had attacks of cramp-like pains in the region of the old scar, and these attacks are now recurring much more frequently. Has lost no flesh or strength; never jaundiced, and bowels regular. On examination, in old appendix wound, there is a small ventral hernia. Palpating through this opening, there is found, at the usual site of the appendix, a hard mass, size of a walnut. Operation, January 10th, 1899. Intestines and omentum matted together and covered with a serous exudate. Several large, hard masses felt in the posterior part of the abdomen, which proved to be retroperitoneal glands. The glands throughout the mesentery were enlarged and hard. Several of these were excised for examination. The appendix was separated from adherent intestines with much difficulty. It was short, thick, and gave evidences of chronic inflammation. The fluid from this region had a foul odor. Appendix removed. Incision closed with drainage.

Pathological number, 4239. Dr. Thacher. October 1st, 1899. Appendix and glands. In some parts of some sections there is a cancerous structure. Some alveoli are round and have a lumen, others are round and packed with cells, others are long and narrow, in places only a single row of cells. Some of the alveoli lie in smooth muscle. There is inflammatory exudation at the surface of some portions. The lymph glands look normal. After-history: This patient was seen in March, 1908, and was in perfect health.

There is a symptomless ventral hernia in the scar, but nothing abnormal is palpable in the iliac fossa. There has been, consequently, no recurrence after nine years.

Fortunately the slides were preserved. I submitted them to Dr. Wood, of Columbia University, on February 20th, 1908, for the purpose of obtaining a photomicrograph, which is here reproduced (Fig. 6). His pathological report is as follows: The specimen consists of three mounted sections of a portion of the intestinal tract. From the thickness of the wall and the fact that there are four or five small gland tubules embedded in the lymphoid tissue, in one portion of one section, it is probable that the material was removed from the appendix. The muscular coats are arranged in a circular and longitudinal group, and scattered irregularly between the muscle bundles are alveoli, filled with irregularly ovoid or polyhedral cells, with large nuclei containing well-marked chromatin. In other portions there is a diffuse infiltration of the muscle tissue with similar cells. At no place has the growth assumed an alveolar type. There are no mitoses visible in the cells. There is only very slight inflammatory reaction around the alveoli containing the cells of the newgrowth. There is no evidence of chronic inflammation of other portions of the tissue. The diagnosis is spheroidal-celled carcinoma of the appendix; whether primary in the appendix or not, it is impossible to say from the sections.*

In connection with these cases, I have gone over the literature and have collected all the reported cases of primary carcinoma of the appendix that I could find after exhaustive search. In 1906, Rolleston and Jones published a report of forty-two cases of malignant tumors primary in the appendix, all doubtful cases having been excluded. Since Rolleston's paper, no collection of such cases has appeared in English. I have found forty-eight cases in all, which in addition to those of Rolleston, make a total of ninety undoubted cases. No case in which the tumor has been found involving the cecum, even to the slightest degree, has been included in either series, because, in such cases, it is impossible to say where the cancer originated, whether in the cecum or in the appendix.

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* That it was primary in the appendix is proved by the material removed at the operation and by the non-recurrence after nine years.

The following is a list of forty-eight cases. The number before each case refers to the corresponding references throughout this article:

I. Landau. Berl. klin. Woch., December 10, 1906.
II. Villar. Gaz. hebdom. des Soc. méd. de Bordeaux, January 3, 1904, p. 3.
III. Weinberg. Bull. et mém. de la Soc. anat. de Paris, 1905, No. 3, p. 38.
IV. Baldauf. Albany Medical Annals, December, 1905.
V. Baldauf. Ibid.
VI. Baldauf. Ibid.
VII. Warthin. Physician and Surgeon, Detroit, December, 1906, p. 544.
VIII. Eccles. Amer. Jour. Med. Sci., June, 1906, p. 966.
IX. Fauldner. Lancet, 1906, i, 598.
X. Brandts. Munch. med. Woch., 1907, September 3, p. 1780.
XI. Brandts. Ibid.
XII. Dreissen. Beiträge zur klin. Chir., 1907, liv, 252.
XIII. Lejars. Bull. et mém. de la Soc. de Chir. de Paris, March 12, 1907.
XIV. Zaaijer. Beiträge zur klin. Chir., liv, 308 (No. 1 of his cases).
XV. Zaaijer. Ibid. (No. 2 of his cases).
XVI. Zaaijer. Ibid. (No. 3 of his cases).
XVII. Zaaijer. Ibid. (No. 4 of his cases).
XVIII. Kaufmann. Spec. patholog. Anat., 1904, 3d edition, p. 464. Case 1.
XIX. Kaufmann. Ibid. Case 2.
XX. Jong. Mitt. aus d. Grenzg. der Med. und Chir., 1907, xviii, Nr. 3.
XXI. Hessberg. Carcinoma Processus Vermiformis, Inaug. Diss., München, 1904.
XXII. McWilliams. This article, p. 1.
XXIII. Zaaijer. Same reference as Cases 14, 15, 16, 17 (his Case No. 5).
XXIV. Zaaijer. Ibid. (his Case No. 6).
XXV. Zaaijer. Ibid. (his Case No. 7).
XXVI. Wiener. This article. Not previously published, p. 8.
XXVII. McCosh. Ibid., p. 4.
XXVIII. Barrow. Georgia Practician, February 15, 1905.
XXIX. Pauchet. Gazette médicale de Picardie, 1900, xviii, 146.
XXX. Nélaton. Bull. et mém. de Soc. de Chir. de Paris, March 12, 1907, p. 228.
XXXI. Hartmann. Ibid., March 5, 1907, Case 1.
XXXII. Hartmann. Ibid., Case 2.

XXXIII. Mason and Rhea. Boston Med. and Surg. Jour., January 10, 1907. p. 44.
XXXIV. Grunbaum. Berl. klin. Woch., August 5, 1907, Nr. 31, p. 984.
XXXV. Patel. Lyon médical, 1907, cix, 276.
XXXVI. Cullingworth and Corner. Lancet, 1904, ii, 1340.
XXXVII. Neri. Beiträge zur path. Anat., 1905, xxxvii, 163.
XXXVIII. de Bovis. Revue de Chir., 1900, p. 708.
XXXIX. Deaver. Amer. Jour. Med. Sci., 1906, p. 845.
XL. Deaver. Ibid.
XLI. Becker. Münch. med. Woch., July 10, 1906, Nr. 28, p. 1383.
XLII. Grieg. Lancet, 1907, ii, 1466.
XLIII. Mandlebaum. Proc. New York Path. Soc., 1905.
XLIV. Mandlebaum. Ibid.
XLV. Korte. Verhand. der Deut. Gesell. f. Chir., 1905, xxxiv.
XLVI. Korte. Ibid.
XLVII. Korte. Ibid.
XLVIII. Libmann. Proc. New York Path. Soc., 1906, No. 6.

I have excluded the following cases because they have either not seemed to be positively cancerous appendices or else not undoubtedly primary in the appendix:

De Ruyter. Archiv. f. klin. Chir., Band lxix, p. 281.
Edington. Glasgow Med. Jour., 1, 120.
Meyerstein. Carcinoma Append. Vermiformis, Inaug. Diss., München, 1905.
Martin. Trans. South. Med. and Surg. Assoc., xvii.
Westerman. Beiträge zur klin. Chir., 1907, liv, 258.
Sudsuki. Three cases of "lymphangitis plastica," Mitt. aus den Grenzg. der Med. und Chir. 1901, vii, 516.

The results of the study of these 48 cases are given in the following pages. In many instances they will be found combined with the statistics of Rolleston, in order that certain facts may be more authoritatively established. In no region of the body are we able to obtain cancers in such an early stage of their development as those occurring primarily in the vermiform appendix, and their careful study should in future elicit new and important information with regard to many points in the life history of malignant neoplasms. Consequently, every case should be accurately observed and reported. Now that attention has been drawn to its occurrence so frequently, it can no longer be considered a curiosity.

Reasons which Led to the Removal of the Appendix.—Of the 48 cases in this series, details are wanting as to this point in 3. Of the 45 remaining cases, 2 appendices were removed at autopsies for other conditions, namely, Case XVIII (Kaufmann), in which the distally enlarged appendix was removed from the body of a woman, aged thirty-one years, who had died in the fourth week of typhoid; and second, Case XXI (Hessberg), in which the primary cancer was found in the appendix of a woman, aged seventy-six years, who had died of general miliary tuberculosis and arteriosclerosis; 36 of the remaining 43 patients suffered from some variety of appendicitis. In Rolleston's series of 33 patients who were operated upon, 27 had symptoms pointing to appendicitis in some form. Thus, out of a total of 76 patients operated upon, 63 (83 per cent.) had had such symptoms. Following the latter's classification, I shall divide these as follows:

1. Symptoms of the first acute attack, operation during or immediately after the first acute attack:
   McWilliams, 13 (Cases 4, 6, 22, 24, 26, 29, 30, 31, 34, 45, 47, 48, 49).
   Rolleston, 10
   Total, 23, or 36.5 per cent.
2. Chronic symptoms without acute attack:
   McWilliams, 8 (Cases 15, 16, 17, 19, 20, 36, 37, 42).
   Rolleston, 5
   Total, 13
3. Chronic with one or more acute attack:
   McWilliams, 2 (Cases 14, 25).
   Rolleston, 3
   Total, 5
4. Recurrent attacks:
   McWilliams:
      Two attacks, 5 (Cases 3, 10, 13, 23, 28).
      Three attacks, 5 (Cases 5. 8, 9, 12, 44).
      Five attacks, 3 (Cases 2, 27, 32).
      Total, 13
   Rolleston, 9
      Total. 22

From these figures we find that of the 63 patients with some variety of appendicitis, 23 (36 .5 per cent.) had their appendices removed during or immediately after the first acute attack. In these cases it would seem more than likely that the growth was the cause of the acute inflammations, acting in a manner similar to a concretion. For the growth may occlude the lumen, causing stagnation of material beyond the tumor with the resulting changes in the mucous membrane, allowing the entrance of micro-organisms, or the same condition may be brought about by ulceration of the surface of the tumor, or its breaking down through lack of nutrition, due to obliteration or compression of the blood vessels. The question then immediately comes up, what causes the growth itself? This will be discussed later.

Forty patients, or 63.5 per cent., had had symptoms of chronic appendicitis in some form for varying periods of time. Of these, 17 are to be found in Rolleston's series, and 23 in my own. I have been able from the imperfect records to ascertain the duration of the symptoms in the following cases:

12 years,	2 cases,	Jones and Simmons, Zaaijer.
7 “	2 “	Weinberg, Kelly and Hurdon.
5 “	1 “	Neri.
4 “	2 “	Hartmann, Jong.
3 “	4 “	Moschkowitz, Driessen, Zaaijer, Villar.
2 “	5 “	Weir, Burnham, Kaufmann, Zaaijer, Mandlebaum, McCosh.
1 “	4 “	Battle, Barrow, Deaver, Eccles.
Many yrs.,	1 “	Kaufmann.
9 months,	1 “	Landau.
7 “	1 “	Baldauf.
3 “	2 “	Lejars, Zaaijer.
2 “	1 “	Cullingworth and Corner.
	—	
	26 cases.	

These figures show that symptoms existed for over a year in 21 patients (more than 28 per cent.). This lends weight to the theory that chronic inflammatory changes are the cause of malignancy.

It would be interesting to inquire, then, in this connection, how many of these appendices, removed from patients with chronic symptoms associated with cancer, showed the microscopical lesions of chronic inflammation? There were 23 patients in my series with chronic symptoms, and associated chronic lesions were found by the microscope in the following cases: Baldauf (V), Eccles (VII), Brandts (X), Driessen (XII), Zaaijer (XIV), Zaaijer (XV), Zaaijer (XVII), Zaaijer (XXV), Deaver (XXXIX), Hartmann (XXXII), Neri (XXXVII), Barrow (XXVIII), Weinberg (III), Mandlebaum (XLIV), Hessberg (XXI), Zaaijer (XXIII), McCosh (XXVII).

Thus, out of 23 cancerous appendices removed for chronic symptoms, in 16 (70 per cent.) it is definitely stated that chronic inflammatory lesions were present in addition to the cancers. In the remaining 7 of the 23 cases, the descriptions of the microscopic findings were either too meagre or too indefinite to judge as to this point.

Are we able to find with the microscope chronic lesions in the cancerous appendices removed from patients in the first acute attack? In my own series of 13 acute cases, I found with regard to this question the following to be the facts:

Case	IV.	Baldauf.	Chronic lesions were stated to be present.
"	VI.	Baldauf.	" " " "
"	XXII.	McWilliams.	" " " "
"	XXIV.	Zaaijer.	" " " "
"	XXIX.	Pauchet.	Not mentioned in record.
"	XXXI.	Hartmann.	" " "
"	XXXIV.	Grunbaum.	" " "
"	XLVII.	Korte.	" " "
"	XLVIII.	Korte.	" " "
"	XLIX.	Libman.	Chronic lesions present.
"	XLV.	Mandlebaum.	" " "
"	XXX.	Nelaton.	" " "
"	XXVI.	Wiener.	" " "

Of these 13 cases, in which cancers were found in appendices removed in the first acute attack, there are 8 (61 per cent.) in which mention is made of chronic inflammatory lesions being found in addition to the cancers.

In 7 of the 48 cases, the primary cancerous appendix was removed in the course of other operations:

Case I. Landau. Myomectomy; left salpingoöphorectomy; appendix removed because of bulbous tip. Chronic lesions also present. Female, aged thirty-three years.

Case VII. Warthin. Acute pelvic abscess, due to pyosalpinx; right salpingoöphorectomy; appendix removed because irregularly thickened. Chronic lesions found with the microscope. Female, aged thirty-two years.

Case XI. Brandts. Symptoms before operation thought to be due to biliary calculi, because of jaundice and recurring pains. Cholecystectomy. Appendix clubbed. Chronic lesions present in appendix. The author says that the "attacks were due to chronic appendicitis caused by the cancer." Male, aged thirty-five years.

Case XX. Jong. Patient had diarrhœal attacks for four years, which were referred to a chronic appendicitis. Removal of the appendix cured the attacks. Appendix found to have a very thick proximal mucous membrane and a stenosis, 2.5 cm. from the tip, which caused a cyst in tip with thick walls. In the appendix, chronic lesions found generally and a cancer in the cyst. Female, aged forty-seven years.

Case XXXIII. Mason and Rhea. In 1903, cyst of ovary removed. In 1905, resection of the tube and ovary for cyst and hydrosalpinx. In 1906, operation for subacute pelvic pains, curettage, ventrosuspension, resection of ovary, and removal of normally appearing appendix, "to prevent any possible further trouble." Chronic lesions present, as well as a small cancer in the tip, only visible by means of the microscope. Female, aged twenty years.

Case XXXV. Patel. Operation for double inguinal herniæ. The right one was tender and irreducible, and contained an adherent appendix. No mention in the record of any lesion except the cancer. Male, aged fifty-eight years.

Case XXXVI. Cullingworth and Corner. Fibromyoma of uterus removed. Appendix amputated because of bulbous tip. Chronic lesions also present. Female, aged thirty-one years.

In these 7 cases, the cancerous appendices were chance findings. The average age of these patients was 36.5 years. Rolleston gives 4 such patients, all operated upon for pelvic lesions.

Summarizing, then, the presence or absence of chronic lesions in my series of 48 cases, I find the following to be the facts:

Among the 23 patients operated upon for chronic appendicitis, 16 were stated to have chronic lesions present, as found by the microscope. Of the 13 patients operated upon for acute appendicitis, 8 were definitely stated also to have chronic lesions present. In 6 of the 7 patients from whom the appendices were removed in the course of other operations, chronic lesions were found. Thus, there was a total of 30 patients out of 48, or 62 per cent., in whose cancerous appendices associated chronic lesions were found by the microscope. Which is primary, the chronic inflammation or the cancer? As yet, there is no correct answer to this question apparently. We may summarize, then, the reasons for the discoveries of the cancers as follows:

	McWilliams.	Rolleston.	Totals.
Acute appendicitis	13	10	23
Chronic appendicitis	23	17	40
Appendices removed in the course of pelvic operations	4	4	8
Iliac fistulæ	0	2	2
Inguinal hernia	1 (Case 35)	0	1
Appendectomy and cholecystectomy	1 (Case 11)	0	1
Appendectomy for chronic diarrhœa	1 (Case 20)	0	1
Autopsies	2	8	10
Unknown	3	1	4
Totals	48	42	90

Frequency of Occurrence of Primary Carcinoma of the Appendix.—This is difficult to ascertain statistically, because in most of the published reports of series of cases, in which the appendices were removed for some reason or another, there is not given the number of appendices which were examined systematically by the microscope; only such cases ought to be included in figures designed to show the relative frequency of primary cancers in removed appendices, because in a large number of cases in my series the tumors were not found except when sections had been examined under the microscope. Many of the appendices containing the cancers were considered at the time of the operations, when viewed macroscopically, to be tuberculous or to be merely the seat of simple cicatrices. The following are reported series of cases with the number of cancerous appendices in each; it is not mentioned in most of the reports just how many of the appendices were examined microscopically:

Baldauf	6 cancers in	735 appendices.
Neri	1 cancer in	82 “
Elting	2 cancers in	320 “
Jong	1 cancer in	255 “
Schrumpf	1 cancer in	150 “
Moschkowitz	6 cancers in	2000 cases.
Zaaijer	4 cancers in	463 “
Kelly (Deaver's cases)	5 cancers in	2500 appendices.*
Total	26 cancers in	6505 appendices or 0.4 per cent.

This frequency of cancer of the appendix differs from the conclusions of Baldauf and of Zaaijer, who maintain that such tumors occur in 1 per cent. of the cases of appendicitis. Their figures are based, however, on a much smaller number of cases than are mine. From my series above, this percentage of Baldauf is altogether too large. It is impossible to judge from the tabulated reports of the above-mentioned authors in what proportion of the cases microscopic examination of the appendices was made. Had such been made in all cases, it is not to be questioned that additional carcinomas would have been found. Until a large number of appendices are examined critically with the microscope, it will be impossible to ascertain correctly just what the true frequency of primary cancer of the appendix is. It is more than likely that many of the cases of cancer of the cecum are due to secondary extensions from a primary growth in the appendix. I have not included any such cases in my statistics.

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* Personal communication from Dr. A. O. J. Kelly. Microscopic examinations were made of all these 2,500 appendices. Not included are two cases of endothelioma.

Age.—In 42 of my series of 48 cases, the ages are known, and are as follows:

	McWilliams.	Rolleston.	Total.	Per cent.
Between 1 and 10 years	2 cases	0	2	3
“ 10 “ 20 “	9 “	7	16	20
“ 20 “ 30 “	16 “	13	29	37
“ 30 “ 40 “	11 “	7	18	22
“ 40 “ 50 “	1 “	5	6	8
“ 50 “ 60 “	1 “	2	3	4
“ 60 “ 70 “	1 “	1	2	3
“ 70 “ 80 “	1 “	0	1	1
“ 80 “ 90 “		1	1	1
—	—	—	—	—
Total......................	42 cases.	36	78	99

Average age 27.7 years.

There were 2 patients aged eight years (Cases VI and X), 1 aged twelve (Case XXIV), 1 aged fifteen (Case XLIX). The oldest patient in my series was aged seventy-six years. It will thus be seen that 27 of the 42 cases, or 66 per cent., of primary cancer of the appendix in my series occurred before the age of thirty. The combined statistics of Rolleston and mine give 47 out of 78 cases, or 60 per cent., as occurring before thirty. The average age in the combined statistics is twenty-nine years.

This is in striking contrast to the age incidence in malignant tumors of the remainder of the intestinal canal. Thus, Rolleston gives, in 41 cases of primary cancers of the duodenum, the average age as fifty-two years; in 9 cases of primary carcinoma of the jejunum and ileum it was 47.2 years; in 30 cases of primary carcinoma of the cecum, 47.8 years; and in 100 cases of primary carcinoma of the remainder of the large intestine, 49.34 years. Thus, we find in 180 cases of cancer of the intestinal canal, exclusive of the appendix, the average age is forty-nine years; while in 77 cases of primary cancers of the appendix the average age is twenty-nine years, which shows that the average age incidence in primary cancer of the appendix is twenty years less than in other parts of the intestine.

Mandlebaum reports that among 96 cases of primary cancer of the intestine occurring in the Mt. Sinai Hospital, New York, 5 were primary in the appendix, or 5.2 per cent. These cases constituted 0.75 per cent. of cancers from all sources. These are undoubtedly very high percentages of frequency, and cannot be accepted as generally typical.

From these statistics, it seems that the age incidence of primary cancer of the appendix corresponds somewhat closely to that of simple appendicitis. Thus, Deaver, in 3,000 cases of ordinary appendicitis, found the following to be the age percentages (I add the percentages in the cancer cases as contrast):

			Simple appendicitis.		Cancer of appendix.	
From	10 to 20	years	27.5	or 69 p. c. before 30	23.0	or 60 p. c. before 30
“	21 to 30	“	41.5		37.1	
“	31 to 40	“	20.1		21.8	
“	41 to 50	“	7.0		7.6	
“	51 to 60	“	2.8		3.8	
“	61 to 70	“	0.6		2.5	
“	70 to 80	“			1.2	
“	80 to 90	“			1.2	

SEX.—These were divided as follows:

	McWilliams.	Rolleston.	Total.	Per cent.
Females	24	20	44	57.1
Males	17	16	33	42.8

From these figures it appears that the disease occurs more frequently in women than in men, the difference in frequency being 15 per cent. in favor of the female sex. It has been suggested that this may be due to the more frequent performance of laparotomy in women than in men. In addition, the proximity of the appendix to the female generative organs, with the possibility of extension to the appendix of irritation induced by inflammation of these organs, may have something to do with its greater frequency among women. Thus, in the 7 cases in my series in which cancerous appendices were removed in the course of other operations, 5 of these occurred in women, 4 of whom were operated upon for pelvic conditions. In Rolleston's 6 cases, operated upon for conditions other than appendicitis, 4 were for pelvic lesions. In a total, then, in Rolleston's and my own series of 13 operations, in course of which the appendices were removed, 8 were upon the female pelvic organs. This brings up the moot question, whether it would not be the part of wisdom in all cases to remove the appendix when one is operating in its vicinity.

Deaver found, in 3,000 cases of ordinary simple inflammations of the appendix, that 62 per cent. occurred in men and 38 per cent. in women. Many authorities maintain that ordinary inflammation in the appendix is the exciting cause of the development of primary cancers in them. If such ordinary inflammations occur in 62 per cent. of the cases in men and 38 per cent. in women, we should naturally expect that these primary cancers of the appendix would be more frequent in men; but the very reverse is the case, for 57 per cent. of primary cancers of the appendix occurred in women and 42 per cent. in men. What is the reason for this reversal of frequency in the two sexes in the two affections? At present there seems to be no explanation whatsoever that adequately answers this question; we must accept it as a fact, to be confirmed or rejected, as the case may be, later by a larger number of cases.

Concretions.—These were mentioned as being present in only 2 cases (X and XXXV). Rolleston found in his series of 42 cases that calculi were present in 3 cases. This makes a total of 5 cases out of 90, or 5.5 per cent. From this we may infer that concretions form a very small rôle, if any, in the etiology of cancer of the appendix, which is in striking contrast to the frequency with which calculi in the gall-bladder are found associated with primary cancer in that organ.

In only 1 recorded case of primary cancer of the appendix is there mention of a foreign body (other than coprolith) having been found. This is Case XXXV (Patel), in which a cancer and a small fish-bone were found in an appendix in an inguinal hernia.

The great rarity (5 per cent.) of fecal concretions in appendices containing primary cancers is in striking contrast to the frequency with which these bodies (not including other foreign bodies) are met with in operations for the removal of the appendix for ordinary inflammatory conditions. Thus, I have collected the following statistics with regard to the frequency of fecal concretions in ordinary appendicitis:

	Cases.	Fecal concretions.
Fitz	300	15
Ranvier	459	179
Murphy	141	43
Deaver	460	74
Schuylenburch	271	36
Hawkes	66	8
Hagen	184	21
Nordman (Korte)	1522	608
Total	3403	984 (or 28.2 per cent.)

Enlarged Glands.—These were mentioned as being present at the time of the operation in only 5 of the cases in my series, or 10 per cent., namely, Case I (Landau), VIII (Eccles), XXVIII (Barrow), XXVI (Wiener), XXVII (McCosh).

In Eccles' case, there were two small glands in the meso-appendix, which, unfortunately, were not examined microscopically. The later history of this patient is not given. In Barrow's case, the mesentery of the ileum, cecum, and part of the ascending colon contained ten or more, both palpably and visibly enlarged glands, one or two of them being as large as an adult thumb. They were deemed tuberculous at the time of the operation, being considered, erroneously, secondary to tuberculosis of the appendix. There was no microscopic examination of these glands. This patient is well at the present time, four years after the operation.

In Landau's case the meso-appendix contained one pea-sized gland, which, on microscopic examination, was found to be free from cancer. The later history of this patient is not given. In Wiener's case (XXVI), a large gland was removed from the mesentery near the ileocecal junction. Microscopic examination showed that it was free from cancer and was merely hyperplastic. This patient was well four years after the operation. In McCosh's case (XXVII), there were many large glands present, but the microscope proved these to be uninvolved by cancer. This patient was perfectly well nine years after the appendectomy.

In 2 cases in my series, Hartmann (XXXI), Baldauf (IV), there were small masses in the meso-appendix which at the time of the operations were considered to be enlarged glands, but which later, on microscopic examination, were found to be metastatic cancerous masses, secondary to the cancers in the appendices, and not cancerous glands.

In Rolleston's series of cases there were three patients in whom the abdominal lymphatic glands were enlarged (the cases of Fiske-Jones and Simmons, Beger, and A. O. J. Kelly). In the case of Fiske-Jones and Simmons, it was found by the microscope that the enlarged mesenteric glands were unaffected with cancer. The patient was well seven months after the operation. Beger's case did not survive the attempt to remove an iliac sinus, due to a cancerous appendix, which had existed for three and a half years. The fistula was found to lead directly into the appendix, which was infiltrated throughout by carcinoma, the growth projecting into the cavity of the cecum, but not actually involving its walls. On post-mortem examination, the retroperitoneal glands were found to have become implicated, but there was no suggestion that the growth in the appendix was other than primary. In the case of A. O. J. Kelly, the peritoneum was studded with very small grayish nodules which suggested miliary tubercles. The patient died on the sixth day as the result of an operation to replace protruding intestines. At the time of the primary operation the retroperitoneal glands were found enlarged (apparently these were not examined microscopically).

Thus, out of 90 cases, only 8 had enlarged glands, or 9 per cent. Of these, in 4 cases the microscope showed that the enlarged glands were not implicated with cancer. In 3 cases the enlarged glands were not examined microscopically. In only one case (1 per cent.) was it positively demonstrated that the glands were cancerous. Hence we must infer that these cancers of the appendix are exceedingly slow in involving the lymphatics. As will be shown later, however, they do spread into the meso-appendix by direct continuity.

Situation of the Tumors.—In 38 of the 48 cases in my series, this is found to be as follows (10 of the records are defective in this regard); Rolleston's series of 33 cases is also added:

	McWilliams.	Rolleston.	Total.	Per cent.
At or near the tip	26	16	42	59.15
In the middle	6	4	10	14.08
Near the base	2	8	10	14.08
At the middle and tip	1	1	2	2.81
Near the base and middle	1	0	1	1.40
Almost the whole appendix	2	4	6	8.44
Total	38	33	71	

From these figures we find that in over 59 per cent. of the cases the tumors were situated at or near the tip, and in 76 per cent. they were located at or distal to the middle. These are striking facts, since it indicates that primary cancers of the appendix develop in the regions where strictures, obliterations of the tip, and chronic inflammatory tissues occur most commonly. One can consequently scarcely refrain from arguing that there may be an etiological connection between these processes and the tumors. Such a relationship is further suggested by finding with the microscope that these cancers often develop directly in these pathological tissues, from which we may possibly infer that the cancer is a new implantation on a prepared ground. These regions, the seats of predilection for cancers, are likewise most exposed to nutritional changes, due to malpositions and twistings, all of which conduce to decadence of tissues.

When all is said that can be said in favor of the view that the chronic inflammation is the precursor and cause of the development of the cancers, no one can deny that the reverse may be true, namely, that the cancer causes the chronic inflammatory changes. To this latter view, it may be objected that the chronic symptoms have, in many of the instances, existed for so long a period of time, years in some of the cases, as to make the existence of cancer for so long a period improbable. This objection, however, may be met by the statement that these primary cancers of the appendix are more than likely of very slow growth, particularly in the beginning. At present we are not in the position of being able to state positively which is primary, the cancer or the chronic changes in the appendix.

Macroscopic Appearance of the Appendices.—Information is afforded by a perusal of the records as to this point in 42 cases. The analysis shows some interesting results:

1. No tumor was present to the naked eye in 14 cases (33.3 per cent.) of the 42 cases. These were Cases 3, 4, 5, 6, 7, 9, 13, 15, 18, 19, 33, 37, 42, 43.

2. A cyst was present in 3 cases (0.7 per cent.); size (*a*) small, No. 20; (*b*) bean, No. 1; (*c*) large, No. 29 (4 inches long by 2⅔ wide, with a twisted pedicle).

3. One or more solid tumors were present in 23 cases (55 per cent.). (*a*) Single tumor, 19 cases: size (1) small, 4 cases, Nos. 24, 25, 36, 39; (2) pea, 13 cases, Nos. 2, 10, 12, 14, 16, 21, 23, 26, 30, 31, 44, 49; (3) bean, 2 cases, Nos. 17, 45. (*b*) Two tumors, 3 cases, Nos. 8, 28, 32. (*c*) Numerous tumors, 1 case, No. 35.

4. Clubbed tip only, 2 cases, Nos. 11 and 34.

5. In 9 cases there were found obliterated areas ("cicatrices") which later under the microscope were discovered to be cancerous cicatrices. These were Cases 3, 5, 7, 14, 21, 25, 33, 36, 37.

6. In 2 cases ulcers were present, Nos. 4 and 6. In both of these cases cancers were found in the ulcers themselves.

7. Perforations were present in 2 cases, Nos. 10 and 22, and concretions were found in 2 cases, Nos. 10 and 35.

8. Four of the cases, all of which had visible small tumors, were thought at the time of the operation to have tuberculous appendices. These were Cases 8, 10, 28, 31. The microscope alone revealed their true nature.

This analysis is interesting to the operating surgeon, for in only 55 per cent. of the cases were visible tumors present. Many of these tumors, however, could not be seen from the outside, as the growths often projected into the lumen without any external prominences, as was instanced in my own case (XXII). In 14, or 33 per cent., no tumors were visible to the naked eye, even after the appendices had been opened throughout. Three of the appendices before they were cut open were erroneously thought to have diverticula as the cause of the prominences at the time of the operations.

From these statistics, then, it is easily seen how fallacious it is to argue that because there is no visible tumor there can be no cancer present; only by careful microscopic examination can possibility of cancer be excluded. Hence the inaccuracy of any statistics based solely on the macroscopic appearances alone of the appendices.

PATHOLOGICAL CLASSIFICATION OF THE TUMORS.—This is a somewhat difficult task, by reason of the different aspects in which this part of the theme has been considered, and on account of the use of a widely varying nomenclature by the authors. I have been assisted in this division by Dr. F. C. Wood, of the Pathological Department of Columbia University, New York, to whom my thanks are due for the assistance, as well as for the photomicrographs which accompany this article.

The following divisions of the neoplasms have been made, based on the microscopic examinations. There are 71 cases in which such examinations are reported:

1. *Columnar-cell Tumors.*– Among these I have also included those which in the records are called adenocancers, cylindrical-cell cancers, and alveolar cancers. There were 14 of this type, or 33 per cent. of the 42 cases in which the variety of cancer was stated in my series of 48 cases. These were Cases 2, 3, 12, 21, 26, 29, 30, 31, 32, 37, 43, 46, 47, 48. The age and sex are stated in 11 cases:

6 females, average age, 39.5 years. 1 was 76 and another 63.
5 males, " " 30.5 years. 2 were 35.
—
11 average age, 35 years.

2. *Spheroidal-cell Cancers.*—Among these are included scirrhus cancers, solid globo-cellular cancers, basal-cell cancers, cancer simplex, polyhedral-cell cancers, carcinoma solidum diffusum, polymorphous-cell, and round-cell cancers. Of these there were 22 cases, or 52.4 per cent. of the 42 cases in my series, in which the variety of neoplasm is stated.

15 females, average age, 23.6 years.
7 males, " " 23.4 "
—
22 average age, 23 years.

These cases were Nos. 1, 4, 5, 6, 7, 8, 10, 13, 15, 18, 19, 20, 22, 24, 25, 27, 33, 34, 36, 44, 45, 49.

3. *Mixed Types.*—Four cases, 1 male, 3 females; average age 29.7 years. (*a*) Scirrhus cancer with intimation of adenocancer, No. 11, male, aged thirty-five years. (*b*) Cancer solidum alveolare partim solidum diffusum, No. 14, female, aged thirty-five years. (*c*) Partly adenocancer, partly cylindrocellulare solidum, partly carcinoma solidum diffusum, No. 16, female, aged twenty-six years. (*d*) Partly adenomatous, chiefly solid and diffuse, No. 23, female, aged twenty-three years.

4. *Columnar-cell cancer*, undergoing spheroidal-cell transformation, 1 case, No. 9, age and sex not given.

5. *Colloid Cancer.*—Case No. 17, male, aged twenty-five years.

6. *Endothelioma.*—None in my series.

7. "*Cancer*" the only designation. Cases 28, 35, 39, 40, 41, 42. Total, 6 cases. In only 3 of these 6 cases are the ages and sex given. There were 2 males with an average age of thirty-eight years and 1 female of seventeen years.

COMBINED STATISTICS,

	McWilliams.	Rolleston.	Totals.	Per cent.	Average age.
Columnar-cell cancers	11	5	16	22.5	43.5
Spheroidal-cell cancers	22	16	38	53.5	23.5
Transitional cancers	1	6	7	9.8	32.7
Mixed cancers	4	0	4	5.6	29.7
Colloid cancers	1	2	3	4.2	
Endotheliomas	0	3	3	4.2	
Total	39	32	71		32.3

From these statistics we see that the spheroidal-cell cancers are 30 per cent. more frequent than the columnar-cell types. There is also a difference of twenty years in the average age incidence in the two varieties of cancer, the average age in the spheroidal-cell cancers being twenty-three years and in the columnar-cell type forty-three years.

If we compare the frequency of these various types of cancer in the remaining portions of the alimentary canal, we find the following to be the case in this regard:

Peterson and Colmers:
Large intestine:

	Per cent.
Adenocancer	86.5
Spheroidal cell	13.5

Kappers and Van Rooyen:
Stomach and intestines:

	Per cent.
Adenocancer	56.6
Mixed forms	13.2
Spheroidal cell	20.7
Colloid	9.5
Intestines alone:	
Adenocancer	72.7

If we compare these figures with those showing the frequency of the different types in appendical cancers, we have a striking contrast.

	Stomach with intestine. Per cent.	Large intestines. Per cent.	Intestines alone. Per cent.	Appendical cancers. Per cent.
Adenocancers	56.6	86.5	72.7	22.5
Spheroidal-cell cancers	20.7	13.5		53.5
Colloid cancers	9.5			4.2
Mixed cancers	13.2			5.6

Hence we see that in the appendical cancers, the columnar-cell, or adenomatous cancers, occur in about one-quarter of the cases only, while in the direct intestinal tract this type of cancer is the rule, occurring in almost three-quarters of the patients. In the stomach and intestines, taken together, the spheroidal-cell cancer is found in only one-fifth of the cases, while in the appendix this type of cancer is found in over one-half of the cases. Colloid cancers of the appendix seem to be rarer than in the other portions of the intestinal tract.

What the significance of these observations is I do not pretend to be able to state or even to speculate about.

A rather striking similarity between the frequency of the occurrence of the various forms of the stomach and appendical cancers is shown when we compare the statistics on this point of 115 cases of stomach cancer reported by Fenwick and the 71 cases of appendical cancers in my series:

	Stomach cancer. Per cent.	Appendical cancer. Per cent.
Columnar-cell	28.6	22.5
Spheroidal-cell	63.3	53.5
Colloid cancer	7.8	4.2

Microscopic Extent of the Growths.—Of the 48 cases in my series, there are records regarding this point in 31 cases, as follows: The neoplasm extended through the mucosa and submucosa alone in 4 cases, or 12.7 per cent., Cases 6, 12, 30, 37. Through the mucosa, submucosa, and muscularis only in 8 cases, or 25.8 per cent., Cases 10, 14, 15, 18, 22, 24, 29, 32. Through the mucosa, submucosa, muscularis, and subserosa in 4 cases, or 12.7 per cent., Cases 5, 11, 17, 33. Through all coats without involvement of the meso-appendix in 8 cases, or 25.8 per cent., Cases 1, 7, 19, 20, 21, 25, 27, 34. Through all the coats with involvement of the meso-appendix in 7 cases, or 22.5 per cent., Cases 3, 4, 13, 16, 23, 28, 31.

From these statistics, then, we find that these appendical neoplasms, when viewed histologically, have a malignant character, showing a tendency to infiltrate progressively contiguous structures (15 cases out of 31, or 48.4 per cent., involving all the coats of the appendices), but without, however, evincing evidences of producing distant metastases or of affecting neighboring lymphatic glands. This invading characteristic is evidently of slow progress, fortunately for the patients. This slow growth is further evidenced by the scarcity of mitotic figures in the sections. In no case are they mentioned as being abundant, the usual designation being "very few."

The malignancy of any tumor is to be judged rather from a clinical than a histological standpoint. Thus we find that rodent ulcer when viewed from a microscopic aspect is a typical carcinoma, and that epulis is a typical sarcoma, yet each clinically has repeatedly been proved to be a fairly benign tumor. The question, then, which particularly interests the operating surgeon is what is the ultimate fate of the patients from whom primary cancers of the appendix have been removed?

Duration of Reported Cures.—The after-histories of a number of the patients have been recorded, and the durations of the cures in the following instances are given:

Well after	9	years,	2 cases,	Jalaguier, McCosh.
“ “	5½	“	1 case,	Driessen.
“ “	5	“	3 cases,	Rolleston, H. Kelly (2 cases).
“ “	4	“	3 “	Wiener, Lecene, Fauldner.
“ “	3	“	4 “	Wier, Warthin, Cullingworth and Corner, Zaaijer.
“ “	2	“	8 “	Moschkowitz, Eccles, Hurdon, Zaaijer, Mandlebaum, Greig, Jong, Thorndike.

Well after 1½ years,	4 cases,	Moschkowitz, Zaaijer (2 cases), McBurney.
“ “ 1 year,	2 “	Battle, Burnham.
“ “ 7 months,	2 “	Zaaijer, Jones and Simmons.
“ “ 6 “	1 case,	Zaaijer.
	30 cases.	

Of the 90 cases in the two series, there were 79 cases operated upon. Of these, 13 were well three years or more after the operations, or 16 per cent., and 21 were well two years or more after the operations, or 26 per cent. Of course, many of the operations were of recent date, and the permanency of the cures is still sub judice.

Prognosis.—It is a remarkable fact that primary cancer of the appendix, which microscopically appears to be a malignant growth, is a relatively benign tumor when viewed clinically, since it does not tend to involve the lymphatics nor to form metastases. Recurrences after operation are almost unknown. This apparent benignity seems to be an exception to the rule that the younger the patient with a malignant growth, the more malignant is that growth. This must simply be accepted as a fact without adequate explanation. Cullingworth and Corner, and also Battle, suggest that perhaps the accompanying inflammation destroys the growth by the sloughing of the offending organ, or the patient dies from peritonitis, or the growth is removed because of the coincident inflammation before dissemination occurs. It must further be remembered that when these growths have become extended, as undoubtedly occurs, they lose all their characteristics as appendical neoplasms, and they are then recognized as cecal cancers only.

In the 79 patients making up the series of Rolleston and my own, who were operated upon, there was only 1 (1.2 per cent.) in which the growth is definitely known to have recurred. This is the case of Lejars. A secondary operation, four months after the first one, showed a cancer of the cecum. The patient succumbed shortly afterward.

An interesting case is related by Lanz[1] of a probable recurrence after operation of a primary cancer of the appendix. It is not included in my series, because there was no microscopic examination of the appendix at the time of the operation. A man, aged forty years, suffered from symptoms of chronic appendicitis. At the operation, the appendix was found adherent and its tip was swollen like a "drumstick." A section of the appendix showed at this latter point a hard tissue mass, which was considered to be a "scar." A recurrence took place, and it was by this only that the true carcinomatous nature of the "scar" was recognized. A similar case is described by De Ruyter[2], in which at autopsy a carcinoma was found to have developed in the stump of an appendix which had been removed six years previously. This case, for a like reason, is not included in my series.

Secondary growths, including cancerous lymphatics, were recognized as occurring in very few cases. In my own series of 48 cases there were only 2 in which mention is made of any such. These were patients of Hartmann (XXXI) and Baldauf (IV), in each of which there was a small metastatic cancerous mass in the meso-appendix. In Rolleston's series of 42 cases there were 4 such cases, namely, Beger's patient, in whom the retroperitoneal glands were implicated, the 2 patients of A. O. J. Kelly and of Elting, in both of whom there were multiple growths on the peritoneum, and Whipham's patient (autopsy), in which there were growths in the liver and right ovary. Thus, we find that in only 6 cases out of 90 in the combined statistics of Rolleston and myself, or 6 per cent., were there secondary growths. From the analysis of the cases in a preceding paragraph, in which there were enlarged glands at the time of the operations, it is seen that because glands are found enlarged, this is no reason for making a bad prognosis, since the microscope showed that only 1 case had cancerous lymphatics, the remainder being merely affected secondarily by simple inflammation from the appendices. Perhaps we may conclude, from the fact that fewer secondary growths were found in my series of cases than in Rolleston's, that appendices are removed more frequently now than formerly was the case for chronic symptoms, and at an earlier date and for slighter symptoms. By so doing, we undoubtedly will in future save a number of patients from developing cecal cancers, secondary to a primary growth in the appendix.

From the facts thus far deduced, it seems as though we should have to place these primary neoplasms of the appendix in a distinct class by themselves, so far as their malignancy is concerned, allying them somewhat in this regard with rodent ulcer and epulis, and in contradistinction to neoplasms of the alimentary tract generally.

Mortality of the Operations.—All the patients in my series recovered after being operated upon, indicating that the presence of primary appendical cancer does not prejudice the operative prognosis per se.

Surgical Significance of Appendical Cancers.—These small neoplasms are not per se to be diagnosticated before operation. The symptoms are those of a simple appendicitis, usually of the chronic, recurrent type. Its age incidence corresponds to that of simple appendicitis. It probably occurs in about 0.4 per cent. of all cases of appendicitis, or 1 in 250, and this fact, if further confirmed in the future, will more surely cause us to advise appendectomy. The seemingly good prognosis of appendical cancers is more apparent than real, for histologically it has a malignant character with a tendency to involve progressively, though probably slowly, the meso-appendix and the cecum. Whether the cancer is the primary lesion and the appendicitis the secondary, or vice versa, makes absolutely no difference from the patient's standpoint. The main thing for him is to be rid of his cancerous appendix at the earliest possible moment.

Such an appendical cancer will almost always first be discovered by an operation. Benign tumors of the appendix are very rare, hence any circumscribed appendical tumor, found at operation, should always make one suspicious of cancer. In doubtful cases, a frozen section, made during the operation, would be of very great advantage, if possible to obtain; and in case of positive findings, a wide excision of the meso-appendix and removal of the lymphatic glands should be practised. If the tumor be situated in the base of the appendix, it would be best to excise part of the cecum, otherwise this would not seem ordinarily to be a necessary procedure. As a frozen section at the time of the operation will rarely be available, it would be the part of wisdom to make a practice of removing habitually the entire meso-appendix in every operation for appendicitis, as this would not increase materially the risk to the patient under ordinary conditions. This practice is rendered advisable, first, because these tumors, even when very small, have a pronounced tendency to invade the meso-appendix; and second, because they frequently are invisible to the naked eye. Every removed appendix should be subjected to a careful microscopic examination.

When operating in the neighborhood of the appendix for reasons other than appendicitis, the appendix should be inspected carefully. If it has an irregular outline, or is clubbed at its extremity, or constricted, or presents a prominence on its surface, it should unhesitatingly be removed. I shall not go into the more debatable question of whether, in operations generally, the appendices should be routinely amputated in the absence of any visible abnormality. It seems, however, advisable to do so provided no extra risk would be incurred, since the appendix is such a potential factor for future harm for the patient in many directions. The practice of removing the appendix close to its junction with the meso-appendix should be deprecated.

RÉSUMÉ.—1. Of the 76 patients operated upon for known reasons, 63 (83 per cent.) suffered from some variety of appendicitis. Of these, 23 (36 per cent.) were operated upon during or immediately after the first acute attack, while 40 patients (63 per cent.) had had symptoms of chronic appendicitis for varying periods of time. Of the entire 79 operated patients, 28 per cent. had had such chronic symptoms for a year or more. Eleven primary cancers of the appendix were found in appendices removed in the course of operations for other purposes, and were chance findings. In 2 other cases, the operations were undertaken for the cure of iliac fistulæ. Ten primary cancers of the appendix were found in the course of autopsies.

2. In 78 cases in which the ages are recorded, it is found that there are 47 patients (60 per cent.) whose age was under thirty years. This age incidence corresponds very closely to that of ordinary inflammatory appendicitis, in which, in 3,000 cases, 69 per cent. occurred before thirty years.

3. In 77 cases of primary cancer of the appendix in which the sex is recorded, we find that there were 44 females (57 per cent.) and 33 males (42 per cent.). In 3,000 cases of simple, inflammatory appendicitis, 62 per cent. occurred in men and 38 per cent. in women. The reason for this almost complete reversal of frequency in the two sexes in the two affections remains as yet entirely inexplainable.

4. Concretions apparently form no rôle in the etiology of primary cancers of the appendix, since in 90 cases they were found only 5 times (5.5 per cent.). This is in sharp contrast to the 984 times fecal concretions were recorded as occurring in 3,403 operations for simple inflammatory appendicitis, or 28 per cent.

5. In 71 cases in which the situation of the tumors was recorded, it is found that in 59 per cent. the neoplasms were located at or near the tip, and in 76 per cent. they were situated at or distal to the middle. This indicates that primary cancers of the appendix develop in the regions where strictures, obliterations of the tip, and chronic inflammatory lesions most commonly occur.

6. Enlarged lymphatic glands were recorded as being present in 8 cases, or 9 per cent. In 4 of these cases, microscopic examinations showed that there was no cancer in them, and in 1 case such

secondary cancerous involvement was found. Hence we must infer that these primary cancers of the appendix are exceedingly slow in involving the lymphatics. Three cases are not recorded as having had the enlarged glands examined microscopically.

7. In 42 cases out of my 48 in which it is recorded, no tumors were visible to the naked eye in 14 cases, or 33 per cent. In 23 cases, or 55 per cent., one or more solid tumors were visible. Cysts were present in 3 cases, or 0.7 per cent. Perforations were present in 2 cases. Ulcerations were found in 2 cases. From these statistics it is evident how fallacious it is to argue that because there is no visible tumor, consequently there is no cancer present. Hence the inaccuracy of any statistics based solely on the macroscopic appearances of the appendices.

8. The frequency of occurrence of primary cancer of the appendix is approximately shown in the fact that 26 such cancers were found in 6,505 appendices, or 0.4 per cent. This percentage is not absolute, because it is not stated in just what proportion of these cases microscopic examination of the appendices was made; presumably such examinations were made in but a small proportion. In addition, cecal cancers undoubtedly develop from primary appendical cancers, in which case the latter lose all their characteristics as the primary lesion, and are overlooked as such. From all of which we may conclude that a conservative estimate would place the occurrence of primary cancer of the appendix as not lower than 0.4 per cent. of all the appendices removed, or 1 in every 258 appendices examined. Positive proof of this estimate can only be established when a large series of microscopically examined appendices is brought forward.

9. In 71 cases it was possible to make a pathological classification of the neoplasms. Twenty-two per cent. were columnar cell cancers, 53 per cent. were spheroidal-cell, 9 per cent. were of the transitional type, and 4 per cent. were colloid cancers. The average age in the spheroidal-cell tumors was twenty-three years

and in the columnar-cell type it was forty-three years, a difference in the age incidence in the two varieties of twenty years. Thus, we see that the spheroidal-cell cancers, primary in the appendix, are 30 per cent. more frequent than the columnar-cell variety. The frequency of occurrence of the two varieties in the appendix is very similar to that in neoplasms of the stomach, while in the intestines alone the columnar-cell type occurs in about 72 per cent. of the cases.

10. Of the 48 cases in my series, there are records regarding the microscopic extent of the growths in the appendices in 31 cases. In 15 cases, or 48 per cent., all the coats of the appendix were invaded, while in 7 cases, or 22 per cent., the meso-appendix in addition was involved in the growth. Thus these neoplasms show a tendency progressively to infiltrate contiguous structures, but without evincing evidences of producing distant metastases. This invading characteristic is probably of slow growth, as is further evidenced by the fact that in all the cases mitotic figures are designated as being very few.

11. Out of 90 patients with primary cancer of the appendix, there were secondary growths present in 6 (6.6 per cent.).

12. In 79 of the patients who were operated upon, the duration of the reported cures is given in 30 instances: 7 patients were well five years or more after the original operations, 13 were in good health three years or more afterward, while 21 showed no signs of any recurrence two years or more after the operations. In only 1 instance out of the 79, or 1.2 per cent., is it definitely stated that the growth recurred. From the facts deduced in this article, it would seem as though these primary tumors of the appendix should be placed in a distinct class by themselves, so far as their malignancy is concerned, allying them somewhat in this regard with rodent ulcer and epulis, and in contradistinction to malignant neoplasms of the alimentary tract generally.

13. The mortality in my series of 46 operations was nil, which indicates that the presence of a primary appendical cancer does not prejudice the operative prognosis per se.

14. The symptoms of these appendical cancers are not sufficiently characteristic to make a diagnosis per se possible without operation.

15. Any circumscribed tumor in an appendix should always arouse suspicions of cancer, following which the meso-appendix should be widely excised and enlarged glands removed. It will be necessary to excise part of the cecum only when the tumor is situated in the base of the appendix.

16. In every appendectomy the entire meso-appendix should be removed if possible.

17. Every removed appendix should be examined microscopically.

18. When operating in the neighborhood of the appendix for reasons other than appendicitis, the appendix should be amputated in case it presents any abnormality, particularly when its tip is clubbed.

19. In addition to the cancers themselves present in the appendices, in 30 cases out of 48 in my series, or 62 per cent., it is found that chronic inflammatory lesions were discovered by the microscope. Whether the chronic changes are primary and the cancers secondary to these, or vice versa, it seems impossible to decide in the present state of our knowledge of the subject.

ADDENDUM.

Since the above article was written, I have found the following additional 33 cases.

Letulle[3] has written a very beautifully illustrated article describing 11 cases which he personally has seen. Two of these are reported in the above article, namely, those of Jalaguier and Nelaton, while the remaining 9 are not so included. Of these 11 cases, only four cancerous appendices were removed at operation, while seven were discovered at autopsy. It is a noteworthy observation that 4 of these latter cases were found in tuberculous patients[4]. Some of these cases illustrate unusual conditions.

Gayet[5] reports a case in which a cancerous appendix was found in a hernial sac, exactly similar to the condition narrated in Patel's case in the above article.

Vassmer[6] relates a case of primary cancer in a gangrenous appendix with peritonitis. The patient died after a secondary enterostomy.

Lubarsch[7] reports the case of a seventeen-year-old boy in the tip of whose appendix, at autopsy, a pea-sized cancer was found.

Weber[8] reports the case of a man, aged forty-three years, who was operated upon for the removal of a ventral hernia, following an operation three years previously for a large appendical abscess. A fist-sized tumor was found in the cecal region which proved to be an adenocancer of the appendix. Recovery.

Lothrop[9] reports operating upon a girl, aged nine years, for an acute gangrenous, perforative appendicitis, with abscess formation. On gross examination, nothing unusual was noticed in the appendix, but later microscopic examination revealed in its centre a primary cancer. The patient recovered. Her youth is noteworthy.

White[10] reports a case of colloid carcinoma of the appendix.

LeConte[11] reports a case in which the entire appendix was invaded by the cancer with involvement of the ileocæcal glands.

Coons[12] found a spheroidal-celled carcinoma of the appendix in a woman of twenty-one years of age. The appendix was removed in the course of an operation for pyosalpinx and ovarian abscess, because it seemed to contain a concretion which could not be dislodged. At the distal end there was found a pea-sized, nodular mass, which was firmly imbedded in the wall of the appendix.

Hammond[13] reports an infiltration carcinoma in the appendix of a man, thirty-five years of age, who was in his eighth attack of appendicitis, the first of which dated back thirteen months.

Garrow and Keenan[14] report two cases, one of which would not have been discovered but for routine examination. One was found in a perforated, gangrenous appendix with abscess.

Monk[15] removed an appendix because of appendicitis, there being no suspicion as to malignant disease until the report of carcinoma of the appendix was returned by the pathologist. There has been no recurrence five and one-half years after the operation.

Harte[16] reports eight cases not given above. In addition he gives résumés of six cases of sarcoma of the appendix.

Day and Rhea[17] publish a case of primary cancer of the appendix in a child, nine years of age.

Elwell[18] describes a case of primary cancer of the appendix, likewise Kepler[19] who gives the literature.

The following unpublished case is kindly given to me by Dr. J. A. Hartwell. He operated upon a woman of thirty-three years of age at the end of her second attack of appendicitis. The appendix was clubbed and inflamed and adherent at the tip. There was no suspicion awakened at the time of the operation of malignancy. There were no enlarged glands. Pathological report: The appendix measured 9 by 1 cm. Serous coat injected. On section canal free, but walls thickened. At tip is a small yellowish growth, occupying the lumen, ½ cm. in diameter. Microscopical examination. There is a growth of fat and connective tissue in submucosa. The mucosa and submucosa of sections from the tip are infiltrated with large, round and oval cells in nests and strands. Diagnosis is carcinoma of appendix.

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VIII.

A CONTRIBUTION TO OUR KNOWLEDGE OF THE ACETONE BODIES, WITH A CLINICAL METHOD FOR THE QUANTITATIVE ESTIMATION OF DIACETIC ACID AND ACETONE.*

By T. Stuart Hart, M.D., Former House Surgeon.

(To this Essay was awarded the Briddon Prize Medal for 1907.)

The scientific and clinical importance of the acetone bodies, viz.: acetone, diacetic and oxybutyric acids, is demonstrated by the many investigations which have been lavished upon them in the last decade. As evidences of disordered metabolism they are of significant value.

The Germans have been the leaders in this promising field of research, but many valuable studies have come from our own countrymen, among which may be recalled the work of Herter, Joslin, Brewer, Baldwin, Hubbard, Brackett, Stone, Low and others.

While much of the earlier work led to conclusions more or less contradictory, the more recent observations permit us to coordinate our knowledge and are full of promise for a rational system of prophylaxis and therapy.

It seems worth while, therefore, to review some of the facts as we know them to-day.

The Relation of the Acetone Bodies to One Another.

The relationship of the acetone bodies is a result of their chemical constitution and is made evident by examining their graphic formulæ.

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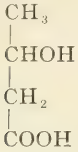
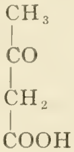
*Reprinted from the Archives of Internal Medicine, February 15, 1908.

B-oxybutyric acid.



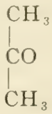
$$\begin{array}{l} CH_3 \\ | \\ CHOH \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

Aceto-acetic acid.
(Diacetic acid)



$$\begin{array}{l} CH_3 \\ | \\ CO \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

Acetone.



$$\begin{array}{l} CH_3 \\ | \\ CO \\ | \\ CH_3 \end{array}$$

By oxidizing oxybutyric acid we obtain diacetic acid, and when diacetic acid is heated to 100° C. it is readily decomposed into acetone and carbonic acid. The latter reaction occurs so readily that hitherto no satisfactory method has been devised of separating the acetone and diacetic acid of the urine, and therefore all quantitative estimations of acetone represent the combined output of diacetic acid and acetone.* By a laborious process we are able, however, to estimate separately the amount of oxybutyric acid.

It seems to be established that oxybutyric acid is the antecedent body from which diacetic acid and acetone are formed. Schwartz[1] has given diacetic acid by mouth to diabetic animals and has seen a partial conversion into acetone in the urine. Geelmuyden[2] gave sodium salts of diacetic acid to normal men, who were on a mixed diet, and a diet without carbohydrates, and found an increase in the acetone output in each instance. Minkowski[3] gave a dog with pancreatic diabetes ten grams of sodium oxybutyric acid, obtaining as a result a large amount of diacetic acid and acetone in the urine.

The relationship of the acetone bodies is also evident, when we consider the order in which they make their appearance in the urine. For example, in a progressive case of diabetes mellitus the first of these bodies which we find is acetone, as the process advances we next detect diacetic acid, and when diacetic acid has increased to a considerable amount oxybutyric acid appears. When a bad case of diabetes begins to improve the acetone bodies

* Recently Follin has proposed a new method for the separation of acetone and diacetic acid (Jour. of Biol. Chem., May, 1907). From a somewhat limited experience with this method, I am inclined to the conclusion that it determines approximately the actual quantitative relationship of these bodies.

disappear in the inverse order in which they occurred; oxybutyric acid is the first to go, followed by diacetic acid and finally by acetone. These sequences, ascending and descending, indicate, respectively, the progressive failure and improvement of oxidation.

Arnold[4] thinks that all the acetone of the urine is excreted as diacetic acid, which is converted into acetone in the urine. He reached this conclusion because, whenever he found acetone in the urine, he also found diacetic acid by means of the test which bears his name. I think his conclusion is incorrect, and that he was led into this error by making use of the comparatively indelicate test of Legal in determining the presence of an acetonuria. As the following table will demonstrate, in a number of my cases I have been able to detect and estimate the quantity of acetone in the urine, without being able to detect diacetic acid either by Gerhardt's or Arnold's reaction, the latter being the most delicate test for diacetic acid which we possess.

Cases Showing Presence of Acetone Without Diacetic Acid.

Case	Date of Examination	Diagnosis	Acetone		Diacetic Acid			
			Lieben's Test	Quantity in Grams	Arnold's	Gerhardt's	Diazo	Riegler's
E. W	14–IV–'05	Cyclic vomiting	+	. . . . . .	0	0	0	0
L. B.	16–V–'05	Diabetes	+	. . . . . .	0	0	0	0
A. C.	12–IV–'05	Diabetes	+	. . . . . .	0	0	0	. .
B. B.	13–IV–'05	Diabetes	+	. . . . . .	0	0	0	. .
E. A. S.	15–IV–'05	Diabetes	+	. . . . . .	0	0	0	. .
C. C. K.	15–IV–'05	Diabetes	+	. . . . . .	0	0	0	0
	25–V–'05	Diabetes	+	0.018	0	0	0	. .
L. H.	7–VI–'05	Diabetes	+	0.021	0	0	. .	. .
M. E. M.	9–V–'05	Diabetes	+	0.017	0	0	0	0

Further, as regards Arnold's contention, it may be said that in diabetes and other conditions a large amount of acetone is found in the breath and diacetic acid is not found in the expired air; therefore it would seem probable that acetone is present as such in the circulating blood and hence would be excreted as such by the kidneys.

When, however, acetone appears in any considerable amount in the urine, diacetic acid can always be detected, and when in turn diacetic acid is evident in large quantities, as for example when we have an exceedingly strong Gerhardt's reaction, oxybutyric acid is always found.

TABLE SHOWING APPEARANCE OF DIACETIC ACID WHEN ACETONE IS EXCRETED IN CONSIDERABLE QUANTITIES.

Case	Date of Examination	Diagnosis	Acetone Tests		Diacetic Acid Tests				Amount of Acetone in 24 hours in grams	Rotation	
			Lieben's	Legal's	Arnold's	Gerhardt's	Diazo	Riegler's		Before fermentation	After fermentation. Indicating presence of Oxybutyric acid
C. C. K.	25–V–'05	Diabetes	+	0	0	0	. .	. .	0.018	. . . . . .	. . . . . .
M. E. M.	9–V–'05	Diabetes	+	0	0	0	. .	0	0.017	. . . . . .	. . . . . .
L. H.	7–VI–'05	Diabetes	+	?	0	0	. .	. .	0.021x	. . . . . .	. . . . . .
B. B.	25–IV–'05	Diabetes	+	+	0	0	. .	. .	0.037x	. . . . . .	. . . . . .
C. C. K.	27–IV–'05	Diabetes	+	+	0	. .	. .	. .	0.060	. . . . . .	. . . . . .
L. B.	10–V–'05	Diabetes	+	+	+	0	0	0	0.068	. . . . . .	. . . . . .
C. C. K.	13–VI–'05	Diabetes	+	+	+	0	0	0	0.399	. . . . . .	. . . . . .
F. J. M.	8–VI–'05	Diabetes	+	+	+	0	0	. .	0.160x	. . . . . .	. . . . . .
G. L.	1–V–'05	Diabetes	+	+	+	+	+	. .	0.800	. . . . . .	. . . . . .
S. C.	5–V–'05	Diabetes	+	+	+	+	+	. .	0.616	. . . . . .	. . . . . .
G. L.	15–V–'05	Diabetes	+	+	+	+	+	?	0.657	. . . . . .	. . . . . .
G. L.	5–VI–'05	Diabetes	+	+	+	+	+	?	1.113	. . . . . .	. . . . . .
S. B. C.	3–V–'05	Diabetes	+	+	+	+	+	. .	1.111x	. . . . . .	. . . . . .
G. L.	8–V–'05	Diabetes	+	+	+	+	+	+	1.333x	+0.5	–1.2
J. F.	12–II–'04	Diabetes	+	+	+	+	+	. .	0.292	+6.0	–1.0
J. F.	22–II–'04	Diabetes	+	+	+	+	. .	. .	0.962	+6.8	–0.4

+ positive reaction, ? doubtful reaction, 0 negative reaction, x amount in one liter.

I think we may look upon the excretion of oxybutyric acid and diacetic acid as invariably due to pathological conditions, and the appearance of any considerable amount of acetone must be regarded in the same light.

Conditions in Which Acetone Bodies Occur.

Recent observation has demonstrated that the excretion of the acetone bodies occurs in a wide number of diseases and under many conditions. In very small amounts acetone may be excreted in the urine in health under normal conditions. v. Engel[5] puts the normal limits at from 0.006 to 0.018 gram of acetone in twenty-four hours. In pathological conditions acetone is thrown off in the expired air as well as in the urine, but diacetic and oxybutyric acids cannot escape by way of the lungs and are excreted by the kidneys alone. There seems to be no constant ratio between the amount of acetone excreted by the kidneys and by the lungs. Schwartz,[6] in some of his determinations, found 70 per cent. of the acetone in the expired breath. The acetone bodies are excreted in considerable quantity in starvation; in certain digestive disturbances; in many febrile diseases such as exanthemata, pneumonia and typhoid fever; after surgical operations; during pregnancy and labor; after the administration of certain drugs, among which are benzol, antipyrin and morphine; following poisoning with phosphorus, phloridzin, atropine, coal gas, curare and lead; in diabetes their amount may be very large. Naunyn[7] reports a case in which there was an output of 188 grams of sodium oxybutyric acid in a single day.

The following table will indicate the various conditions under which acetone bodies are excreted, with the maximum amounts, as noted by numerous observers:

CONDITIONS UNDER WHICH THE ACETONE BODIES ARE EXCRETED.

Condition or Disease	Acetone	Diacetic Acid	Maximum amount of Acetone in twenty-four hours. Estimations include Diacetic acid		Oxybutyric acid	Amount of Oxybutyric acid in twenty-four hours	Observer
			Urine	Breath			
Normal	+	....	0.010	....	....	....	v. Jasch.
Normal	+	....	0.015	....	....	....	Boeri.
Normal	+	....	0.018	....	....	....	v. Engel.
Normal	+	....	......	0.023	....	....	Müller.
Starvation	+	....	0.703	....	....	....	Hirschfield.
Starvation	+	....	0.784	....	....	....	Müller.
Starvation	+	+	......	....	+	2.98	Waldvogel.
Starvation	+	+	0.699	....	+	1.60	Waldvogel.
Starvation	+	....	0.431	0.469	....	....	Joslin.
Starvation and oleic acid	+	....	0.926	0.847	....	....	Joslin.
Digestive disturbances	+	+	......	....	+	....	Lorenz.
	+	+	......	....	+	....	Magnus-Levy.
Diarrhœa	+	+	4.000	....	....	....	Beauvy.
Auto-intoxication	+	+	0.500	....	....	....	Beauvy.
Appendicitis	+	+	0.400	....	....	....	Beauvy.
Typhoid	+	+	1.000	....	....	....	Beauvy.
Typhoid	....	....	......	....	+	....	v. Noorden.
Erysipelas	+	+	0.800	....	....	....	Beauvy.
Variola	+	+	0.500	....	....	....	Beauvy.
Varicella	+	+	0.600	....	....	....	Beauvy.
Measles	+	+	0.800	....	....	....	Beauvy.
Measles	....	....	......	....	+	....	Külz.
Scarlatina	+	+	0.700	....	....	....	Beauvy.
Otitis	+	+	0.500	....	+	....	Beauvy.
Diphtheria	+	+	0.700	....	....	....	Beauvy.
Pneumonia	+	+	1.000	....	....	....	Beauvy.
Tubercular meningitis	+	+	0.600	....	....	....	Beauvy.
Anæsthesia	+	+	......	....	+	....	Waldvogel.
Diabetes mellitus	+	+	10. +	....	....	....	Naunyn.
Diabetes mellitus	+	+	19.000	....	....	....	Magnus-Levy.
Diabetes mellitus	+	+	4.200	3.600	....	....	Schwartz.
Diabetes and mixed diet	+	+	......	....	+	12.1	Wolpe.
Diabetic coma	+	+	......	....	+	22.8	Wolpe.
Diabetic coma	+	+	......	....	+	16.0	Minkowski.
Diabetic coma	+	+	......	....	+	188.0	Naunyn.
Diabetic coma	+	+	......	....	+	100.0 to 150.0	Magnus-Levy

SOURCE OF ACETONE BODIES.

While, on theoretical grounds, it is quite possible that the acetone bodies may be derived from proteids, from carbohydrates, and from fats, the evidence of observation and experimentation very strongly indicates that the fats are the chief antecedent of oxybutyric acid, and its oxidation products, diacetic acid and acetone. We cannot, in this place, discuss all the evidence for the above statement, but may mention briefly some of the findings.* The theory of the proteid origin meets with many difficulties; there is no parallelism between the amounts of proteid destruction, as represented by the output of nitrogen, sulphates and phosphates, and the amount of the acetone bodies excreted; in certain cases it has been found that even when the proteid metabolism is excessive a larger amount of oxybutyric acid is excreted than could possibly be made from the whole amount of proteid broken down. As regards carbohydrates, their withdrawal from the diet is almost invariably followed by an increase in the output of acetone, and when administered to those who can utilize them a reduction in the acetone excretion immediately follows.

When we consider the facts which point to the fats as the source of the acetone bodies, the evidence is much more conclusive. The amount of acetone bodies excreted varies directly with the amount of fat broken down. The feeding of considerable amounts of fat, in cases of starvation and diabetes, and to those who have been kept for some time on a fat-proteid diet, and even, at times, to subjects on a mixed diet, is followed by an increased excretion of acetone. On an exclusive proteid diet an acetonuria usually occurs, but in this case the source of the acetone is undoubtedly the body fat. It seems to be practically proved that the formation of the acetone bodies is the direct result of the improper oxidation of fat, either the fat of the food, or the fat of the body.

FAT SPLITTING IN THE BODY.

Normally fats are oxidized in the body to carbonic acid and water. It is still, however, to be settled by investigation as to whether the acetone bodies are normal intermediary products of fat metabolism, which for some reason fail to be further oxidized to carbonic acid and water, or whether, in these conditions, the splitting of fat follows a pathological course.

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* For a full discussion of this subject, see Hart, American Journal of the Medical Sciences, August, 1906.

One of the most prominent factors, upon which depends the failure to properly and completely oxidize fats, is the absence of carbohydrate food, or the inability to utilize sugars and starches, as in diabetes mellitus. In many cases the administration of a small amount of carbohydrate food will immediately be followed by a disappearance of the acetonuria which is present. Some authors (Naunyn,[8] Geelmuyden,[9] etc.) believe that the oxidation of the acetone bodies is completed by a simultaneous combustion of carbohydrates and a direct union of the acetone bodies with the carbohydrate derivatives.

However, it seems to be quite certain, that in conditions in which acetone bodies are excreted in very large amounts (*e. g.*, poisoning with carbonic acid gas, poisoning with phloridzin, exclusive feeding on animal fats, extirpation of the pancreas, and in severe diabetes) the capability of the organism to burn these substances, when administered by the alimentary canal or subcutaneously, is considerably reduced. The healthy organism will practically completely oxidize oxybutyric acid when given by mouth or subcutaneously, but when given in the above abnormal conditions it is excreted as oxybutyric acid, diacetic acid and acetone.

While, therefore, the absence of carbohydrates may, in a large measure, account for the incomplete combustion of fats, it seems probable that in some of these conditions the organism has lost its power of completely burning fats, in a manner not to be explained by the absence of carbohydrate alone.

A Definition of Diabetes Mellitus.

The above conception as to the origin and mode of formation of the acetone bodies has an important bearing on the functional disturbances underlying many diseases.

For example, it leads one to define diabetes mellitus as a disease of faulty metabolism, in which there is not only an incomplete combustion of carbohydrates, but also an inability to burn fats. For, in every case of advanced diabetes, we find an excretion of some one or all of the acetone bodies, and this means, in the light of what has been said, that the diabetic is unable to properly oxidize fats.

Importance and Practical Value of Estimating the Acetone Bodies.

If acetone bodies are excreted in any considerable quantity, they are positive evidence of improper metabolism. Their study is not only of value because it furnishes us with knowledge important in making a correct diagnosis and prognosis, but also because it affords us a means of following our patient's condition from day to day, and of estimating the value of the therapeutic measures which we are using.

In following a case of diabetes mellitus observations on the acetone body excretion are as important as a knowledge of the sugar output. As soon as diacetic acid appears in the urine, however small may be the amount of glucose excreted, we should recognize that an improper metabolism of fat is in progress. The appearance of oxybutyric acid indicates that the body cells are burning their fuel even less well, that a condition of acid intoxication is imminent, and that coma, however remote, may threaten at any moment.

Recent observations on acid intoxication during confinement and following surgical operations make their estimation of importance in these conditions.

Such studies should be useful in estimating the value of the dietary of large institutions. Here the alienist may find evidence of starvation in cases in which it is suspected but unproved.

Knowledge of the progress of acetone body excretion is of value in all chronic diseases with tissue destruction, and in acute disease with rapid wasting.

I think that from what has been pointed out it will be conceded that the estimation of the acetone bodies is important and of wider application than is usually supposed.

A Clinical Method of Estimating the Acetone Bodies.

For the purpose of following the acetone body excretion at short intervals in general practice the usual quantitative methods are too laborious. Furthermore, as it has already been pointed out in many cases, a very large part of the acetone is excreted by the lungs, the determination of the acetone of the breath is an undertaking impossible in general practice, but unless this is estimated the exact quantitative determination of the amount of acetone in the urine is in itself of little value. If, however, we could estimate the acetone bodies excreted by the kidneys by means of a short, simple method, which required little time and was approximately accurate, it would afford us knowledge of great value in following quantitatively the changes from day to day. The need of such a method has induced the present study and has led me to devise a simple clinical method based on the delicacy of the well-known test-tube reactions in urine containing the acetone bodies.

The following conclusions are based on the examination of over 600 specimens of urine for the acetone bodies. In 350 of these comparative tests were made with Lieben's, Legal's, Arnold's, Gerhardt's and Ehrlich's diazo tests; in a few Frommer's, Riegler's, Lipliawsky's and Lindemann's reactions were also employed. Quantitative acetone determinations were made in over 100 specimens by the Huppert-Messinger method. Oxybutyric acid was tested for by determining the laevo-rotation after fermentation. Of the 350 specimens in which comparative tests were made

250 were from diabetics; the remaining 100 were from miscellaneous cases, including starvation, abdominal neoplasms, cyclic vomiting, pregnancy, operative cases, obesity, febrile (grippe, tonsillitis, typhoid, pneumonia, cerebro-spinal meningitis) and normal cases.

The reactions finally selected on account of their relative delicacy and ease of application were as follows:

For Acetone.

1. *Lieben's Test:* 5 cc. of commercial hydrochloric acid added to 50 cc. urine and distilled; to the first 5 cc. of the distillate there are added 5 drops of a 30 per cent. solution of sodium hydrate and 10 drops of iodo-potassic iodide solution. If acetone is present, a yellowish precipitate of iodoform will be thrown down, which may be recognized macroscopically, or under the microscope, if present only in traces. This will detect acetone when present only in traces found in normal urine, viz., under 0.020 gram to the liter.

Unless special precautions are taken[10] alcohol and aldehyde will precipitate iodoform in the same manner, therefore this should be borne in mind as a possible error.

2. *Legal's Test:* To 5 cc. of the native urine there are added 5 drops of a freshly prepared 20 per cent. watery solution of sodium nitro-prusside, and 5 drops of 30 per cent. solution of sodium hydrate. This is poured into a white porcelain dish and glacial acetic acid added, drop by drop. The development of a purplish color indicates the presence of acetone.

This will detect acetone when present in amounts over 0.030 gram to the liter, *i. e.*, whenever acetone is present in pathological quantities. A positive Legal's reaction is also given by urines containing creatinine in considerable amounts, aldehyde and alcohol.

For Diacetic Acid.

3. *Arnold's Test:* Two solutions are necessary. The first is made by dissolving one gram of para-amido-aceto-phenon in 100 cc. of distilled water and adding hydrochloric acid, drop by drop, until the solution, which at first is yellow, becomes colorless; an excess of the acid should be avoided. The second is a one per cent. watery solution of sodium nitrite. Mix 2 cc. of the para-amido-aceto-phenon solution with 1 cc. of the sodium nitrite solution, to this add 3 cc. of the urine to be tested, then 3 drops of strong ammonia. This is poured into a white porcelain dish and an excess of concentrated hydrochloric acid is added. In the presence of diacetic acid a purplish-violet color appears, which may be readily seen against the white porcelain.[11]

In my hands this has proved the most delicate reaction for the detection of diacetic acid which we possess. Lipliawsky's modification takes a little more time and seems to be no more delicate. Arnold's test does not react to acetone or β-oxybutyric acid, nor is the color developed in the urine of patients taking salicylic acid compounds.

4. *Gerhardt's Test:* In this a stock solution of 50 grams of ferric chloride dissolved in 50 cc. of distilled water is used. One cubic centimeter of this solution is added to 10 cc. of urine. In the presence of diacetic acid in considerable amounts a purplish red color is developed.

This is not as delicate a test as Arnold's. Gerhardt's reaction also occurs in the urine of patients taking the salicylic compounds, phenacetin, antipyrine, etc.

In my routine work I have come to make use of the above mentioned four simple reactions. Frommer's test[12] has not, in my hands, proved satisfactory; it seems to answer fairly well to detect acetone when it is present in large amounts, but the color reaction is uncertain and exceedingly slow when only small quantities of acetone are present. Ehrlich's diazo reaction, as first pointed out by Munson and Oertel,[13] is a fairly good test for diacetic acid, but is neither as reliable nor as delicate as Gerhardt's test.* Riegler's test[14] for diacetic acid is less delicate than the ferric chloride test. The same may be said for Lindemann's test.[15]

In the 500 specimens of urine examined, whenever diacetic acid was found, acetone was invariably present. A much smaller number were examined for oxybutyric acid; whenever this was present the specimen invariably contained both diacetic acid and acetone. I believe we may feel positive that, whenever oxybutyric occurs in the urine, it is always associated with acetone and diacetic acid. With an excretion of diacetic acid there is always an acetonuria. Reversely, however, we may have acetone without diacetic acid or oxybutyric acid; or acetone and diacetic acid without the excretion of β-oxybutyric acid.

We have at present no satisfactory means of estimating the amount of diacetic acid in the urine. All quantitative estimations of acetone represent acetone plus diacetic acid (if this is present) in terms of acetone. Oxybutyric acid may be accurately estimated by a laborious process, or may be roughly determined by the degree of polariscopic laevo-rotation after fermentation.[16]

In the above series a great many quantitative acetone determinations were made, with the purpose of obtaining, if possible, a simple method of following the increase and diminution, clinically, of the acetone bodies. A few of the typical results, which could be greatly extended, if space would allow, are shown in the table on the following page:

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* The diazo reaction as found in typhoid fever is not usually due to the presence of diacetic acid, as Oertel and Munson claimed. It may occasionally be due to diacetic acid, but usually is due to some other substance.

Name	Date	Acetone		Diacetic acid		Oxybutyric acid	Acetone	
		Lieben's	Legal's	Arnold's	Gerhardt's		Grams per liter	
C. C. K.	25-V-'05	+	0	0	0		0.014	Lieben's positive, Legal's negative. Acetone is less than 0.030 gram to one liter.
M. E. M.	9-V-'05	+	0	0	0		0.015	
E. R. W.	26-III-'06	+	0	0	0		0.019	
N. R.	24-IX-'05	+	0	0	0		0.029	
L. H.	7-VI-'05	+	?	0	0		0.021	Lieben's and Legal's positive, Arnold's negative. Acetone is present in an amount from 0.030 to 0.100 gram to one liter.
E. R. W.	12-III-'06	+	+	0	0		0.031	
S. M.	5-I-'06	+	+	0	0		0.031	
E. R. W.	29-I-'06	+	+	0	0		0.040	
C. C. K.	27-IV-'05	+	+	0	0		0.039	
B. B.	25-IV-'05	+	+	0	0		0.037	
E. S.	29-XI-'05	+	+	0	0		0.080	
E. R. W.	2-III-'06	+	+	+	0		0.100	Arnold's positive; Gerhardt's negative. Acetone is present in an amount from 0.100 to 0.200 gram per liter.
C. C. K.	13-VI-'05	+	+	+	0		0.155	
F. J. M.	8-VI-'05	+	+	+	0		0.160	
C. C. K.	18-XII-'05	+	+	+	+		0.214	Lieben's, Legal's, Arnold's and Gerhardt's all positive. Acetone is present in an amount greater than 0.200 gram to one liter.
C. C. K.	13-I-'06	+	+	+	+	+	0.331	
G. H. M.	16-VI-'06	+	+	+	+		0.340	
G. L.	1-V-'05	+	+	+	+		0.500	
A. B.	29-I-'06	+	+	+	+		0.640	
G. L.	1-I-'06	+	+	+	+		0.700	
G. L.	19-III-'06	+	+	+	+		0.800	
N. R.	7-12-'05	+	+	+	+		0.888	
S. B. C.	3-V-'05	+	+	+	+		1.111	
G. L.	8-V-'05	+	+	+	+	+	1.333	
G. L.	8-I-'06	+	+	+	+	+	3.200	
J. F. M	3-I-'06	+	+	+	+	+	4.000	

From this table it is evident that there is a fairly definite relationship between the delicacy of the above reactions and the amount of diacetic acid and acetone present, estimated as acetone. This relationship holds good only for fairly fresh urines; after standing for two or three days diacetic acid is broken down into acetone, and the amount of acetone estimated is greater than is indicated by the application of the above tests.

When we come to consider a simple method for estimating the acetone bodies, when they are present in larger amounts, we meet with the difficulty, that the relative amounts of acetone and diacetic acid in these cases are very variable. A rough idea, however, can be obtained in the following manner:

To ten cubic centimeters of the urine to be tested is added one cubic centimeter of Gerhardt's test solution of ferric chloride (made as described above). This is thoroughly mixed and allowed to stand for about two minutes (to permit the color reaction to fully develop); this is then filtered into a test tube one-half inch in diameter and the color compared with a similar test tube filled with the standard solution of ferric chloride above described. If the color of the urine mixture is darker than that of the ferric chloride solution, distilled water is added until the color is approximately of the same depth as that of the ferric chloride solution.

From the table below, made from a number of specimens examined in this way, a rough idea may be obtained of the amount of acetone and diacetic acid, in terms of acetone, which such dilutions indicate.

Name	10 cc. Urine + 1 cc. standard ferric chloride solution diluted with distilled water to—	Diacetic acid and acetone in terms of acetone per liter in grams	
E. P. A.	undiluted	0.200	All cases of Diabetes Mellitus.
R. B.	undiluted	0.250	
E. A. S.	undiluted	0.500	
J. W. T.	undiluted	0.532	
S. B.	20 cc.	0.400	
J. W. T.	20 cc.	0.424	
J. W. T.	20 cc.	0.532	
A. E. S.	30 cc.	2.500	
M. B.	30 cc.	2.664	
F. R.	40 cc.	2.575	
L. D.	50 cc.	2.665	
M. B.	50 cc.	3.200	
G. L.	60 cc.	5.000	
M. F.	90 cc.	13.330	
G. L.	120 cc.	12.800	

The practical application of this method is conducted in the following manner: The urine under examination is tested by Gerhardt's reaction. If this is positive, we know that diacetic acid and acetone are present in an amount, in terms of acetone, in excess of 0.200 gram per liter. If there is a strong Gerhardt's reaction we dilute the test solution in the manner described above until the color approximates that of the standard ferric chloride solution.

If the final dilution indicates an acetone content of half a gram per liter, or over, we may be reasonably sure that oxybutyric acid is present, and may proceed to its determination by means of the polariscope. If Gerhardt's test is negative we apply successively Arnold's, Legal's and Lieben's tests, in the order named. A positive Arnold's reaction indicates something over 0.100 gram of acetone per liter. A positive Legal's reaction indicates 0.030 gram of acetone per liter. Lieben's test, if positive while Legal's is negative, indicates the presence of acetone in an amount within the normal limits.

Lieben's	Legal's	Arnold's	Gerhardt's	Amount of acetone in gram per liter
Positive	0	0	0	Less than 0.030
....	Positive	0	0	0.030 to 0.100
....	....	Positive	0	0.100 to 0.200
....	....	....	Positive	More than 0.200

The above tests, with the exception of the polariscopic determination of oxybutyric acid, and the distillation required by Lieben's test, may be easily completed inside of ten minutes.

The following charts indicate the method of recording cases and the comparative results obtained by actual quantitative determinations of acetone by the Huppert-Messinger method.

CASE OF OBESITY (REDUCTION TREATMENT)

Date	Amount 24 hours cu. cm.	Specific Gravity	Reaction	Albumen	Acetone		Diacetic Acid		Acetone grams per liter	Acetone grams 24 hours	Urea grams 24 hours	Weight	Diet
					Lieben's	Legal's	Arnold's	Gerhardt's					
1906													
Jan. 29	1825	1026	ac.	0	+	0	0	0	0.040	0.073	25.5	241	Mixed.
Feb. 4	1550	1021	ac.	0	+	+	+	0	....	....	15.5	237	No carbohydrates.
Feb. 9	1700	1019	ac.	0	+	+	+	+	0.800	1.360	27.2	235	Fat-proteid + 100 grams wheat bread.
Feb. 12	1350	1025	ac.	0	+	+	+	0	....	....	24.2	233½	Fat-proteid + 200 grams wheat bread.
Feb. 20	1215	1022	ac.	0	+	+	0	0	....	....	24.3	230	Fat-proteid + 100 grams rye bread + grape fruit
Mar. 2	1320	1024	ac.	0	+	+	0	0	0.100	0.132	26.4	226¼	Same.
Mar. 12	1560	1023	ac.	0	+	?	0	0	0.031	0.048	34.3	224¼	Same + 1 apple.
Mar. 26	1440	1026	ac.	0	+	0	0	0	0.019	0.027	34.6	228½	Same + 1 apple.
Apr. 23	1410	1021	ac.	0	+	0	0	0	....	....	....	216	Fat-proteid + 200 grams wheat bread.

Loss of weight in three months 25 pounds.

FEVER CASE.

Date 1906	Amount 24 hours	Specific Gravity	Reaction	Albumen	Sugar	Indican	Diazo	Acetone		Diacetic acid		Acetone Grams per liter	Acetone Grams in 24 hours	Temperature	Diet
								Lieben's	Legal's	Arnold's	Gerhardt's				
Apr. 16	....	1026	ac.	0	0	0	0	+	+	+	+	1.132	....	101½°	Fluids.
Apr. 18	385	1023	ac.	0	0	0	0	+	+	+	+	0.280	0.098	100½°	Fluids.
Apr. 19	440	1023	ac.	0	0	0	tr.	+	+	+	+	0.300	0.132	100°	Fluids.
Apr. 20	770	1011	ac.	0	0	0	0	+	+	+	0	0.125	0.096	98.8°	Chop, egg, bread.
Apr. 23	....	1016	ac.	0	0	0	0	+	+	0	0	......	....	98.6°	Full mixed.

CASE OF CYCLIC VOMITING.

Date 1905	Acetone		Diacetic acid		
	Lieben's	Legal's	Arnold's	Gerhardt's	
April 12	+	+	+	+	Height of attack
April 13	+	+	+	0	Less severe
April 14	+	0	0	0	Still better
April 15	0	0	0	0	End of attack

VERY SEVERE CASE OF DIABETES MELLITUS.

Date	Amount in 24 hrs.	Specific gravity	Reaction	Albumen	Sugar			Polarization			Acetone		Diacetic acid		Oxybutyric acid	Ammonia	Urea, grams in 24 hours	Weight	Acetone	
					Fehling's	Fermentation	Grams in 24 hours	Before ferment	After ferment	Difference	Lieben's	Legal's	Arnold's	Gerhardt's					Grams per liter	Grams in 24 hours
1904																				
Oct. 10	1380	1031	ac.	0	+	+	69.0	.....	....	....	+	+	0	0	....	1.17	23.5	130	......	......
1905																				
Mar. 13	1100	1028	ac.	0	+	+	7.7	.....	....	....	+	+	+	+	....	....	30.8	139.	......	......
Apr. 10	1000	1029	ac.	0	+	+	6.9	.....	....	....	+	+	+	+	....	....	30.0	137.	......	......
May 1	1600	1028	ac.	0	+	+	18.4	+0.3	-0.8	1.1	+	+	+	(20)	+	....	....	136.5	0.500	0.800
May 8	....	1029	ac.	0	+	+	.....	+0.5	-1.2	1.7	+	+	+	(30)	+	....	....	......	1.333	......
May 15	1200	1022	ac.	0	+	+	.....	.....	....	....	+	+	+	(20)	....	....	....	......	0.598	0.657
June 5	1300	1028	ac.	0	+	+	20.8	.....	....	....	+	+	+	(20)	....	....	....	136.	0.856	1.113
Dec. 18	1500	1025	ac.	0	+	+	30.0	.....	....	....	+	+	+	(20)	....	....	19.5	128.5	0.700	1.050
1906																				
Jan. 1	....	1030	ac.	0	+	+	.....	.....	....	....	+	+	+	(20)	....	....	....	......	0.664	......
Jan. 8	1560	1030	ac.	0	+	+	9.36	.....	....	....	+	+	+	(50)	....	....	21.8	127.	3.200	4.992
Mar. 19	....	1027	ac.	tr.	+	+	.....	.....	....	....	+	+	+	(20)	....	....	....	126.	0.800	......
May. 31	....	1023	ac.	0	+	+	.....	.....	....	....	+	+	+	(120)	....	....	20.7	111.	12.800	......
June 4	2300	1023	ac.	tr.	+	+	143.8	.....	....	....	+	+	+	(60)	....	....	....	......	6.400	14.720
June 11	3210	1024	ac.	tr+	+	+	106.9	+3.2	-0.9	4.1	+	+	+	(60)	57.8	6.55	32.1	108.2	5.000	16.050
July 7	2940	1029	ac.	tr.	+	+	123.0	+3.7	-0.5	4.2	+	+	+	(40)	29.4	3.68	18.8	106.	......	......
July 13	1900	1026	ac.	tr.	+	+	45.6	+1.4	-1.0	2.4	+	+	+	(50)	38.0	4.39	20.0	105.	......	......
July 29	3340	1028	ac.	tr.	+	+	100.0	.....	....	....	+	+	....	(100)	....	....	....	......	......	......
Aug. 14	3000	1025	ac.	tr.	+	+	81.0	.....	....	....	+	+	....	(70)	....	....	....	......	......	......
Sept. 1	3700	1025	ac.	tr.	+	+	130.0	.....	....	....	+	+	....	(80)	....	....	....	......	......	......

Died in coma Sept. 15, 1906.

( ) Number of cubic centimeters to which Gerhardt's test was diluted (as described).

I wish to express my obligation to Dr. E. G. Janeway, in whose laboratory this work was conducted, and to whom I am indebted for a large part of the material upon which these observations were made.

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IX.

THE ETIOLOGY OF ACUTE RHEUMATIC FEVER.

By J. C. Meakins, M.D., Resident Pathologist.

The name acute rheumatic fever is preferable to acute articular rheumatism since the disease is not simply an affection of the joints but involves many parts far distant from these structures. The significance of its many manifestations can be properly understood only when it is considered a systemic disease. Acute articular rheumatism was first described as a distinct entity early in the seventeenth century, when it was distinguished from gout. The next step in the proper understanding of this disease was the recognition of its close relation to chorea. In the early part of the last century several observers called attention to the frequency of cardiac complications and such complications were soon looked upon as manifestations of this disease. The conception that acute rheumatic fever is a systemic disease has gradually found acceptance, but this opinion has been hampered by perpetuation of the name, acute articular rheumatism, even though acute rheumatic fever may exist without lesions of the joints.

The etiology of acute rheumatic fever has been explained by different theories. It has been thought that the disease is due to cold, dampness and changes of temperature. J. K. Mitchell has advocated the theory that it is caused by a lesion of the central nervous system and the disease has been localized in a hypothetical joint centre. A chemical theory of rheumatism has been advanced chiefly by the English writers, and to lactic and uric acids have been given preëminent places. The toxic theory of the disease ascribed it to intestinal putrefaction and the absorption of the toxins so formed. In 1888, however, a new conception of acute rheumatic fever had its origin when Cheadle conclusively demonstrated that arthritis was only one manifestation of a general disease. With the advance of bacteriology the close resemblance between acute rheumatic fever and other infectious diseases was observed. Achalme[1] described a bacillus which he isolated from the joints in a case of acute arthritis. Singer,[2] Sahli,[3] Maragliano[4] and others regarded staphylococcus aureus as the cause of acute rheumatic fever.

Dana,[5] Charrin[6] and Lubarsch[7] isolated a diplococcus or streptococcus from cases of acute rheumatic fever. In 1899 Wassermann and Westphal[8] published an exhaustive experimental study of a streptococcus which they isolated from a case of chorea following acute rheumatic fever, and with this organism they produced polyarthritis in rabbits.

Since 1900 a most important and exhaustive study of acute rheumatic fever has been made by British investigators, chief among whom are Poynton and Paine[9], Beattie[10] and Shaw.[11] They have repeatedly isolated before and after death a diplococcus from the fluids and tissues of individuals who have suffered from acute rheumatic fever. This organism they have named "Diplococcus rheumaticus." They have grown it from the blood, urine and pleural exudate during life from patients with acute rheumatic fever, and from the heart valves and the pericardial fluid after death. They have also demonstrated it in sections of the heart valves and pericardium and of a rheumatic nodule from a fatal case of acute rheumatic fever.

Rapidly accumulating facts afford evidence that acute rheumatic fever is a bacterial infection and that the organism is a streptococcus. That this organism is a distinct variety of the streptococci has yet to be proven. Bacteriologists are not willing to classify streptococci as streptococcus erysipelatis, pyogenes and rheumaticus, or as streptococcus brevis and longus. It is true that streptococci do cause, at times, certain well defined diseases;

they vary in the length of the chain which they form. Are these essential differences on which a definite classification may be based? Can it be said that a streptococcus which produces erysipelas will not also produce rheumatic lesions? The following case will illustrate the fallacy of such opinions:

The patient, R. E., entered the Presbyterian Hospital under the service of Dr. Thompson, to whom I wish to express my thanks for permission to report the clinical history. The patient was a male, age 17, single, laborer, white. *Family History:*—One sister has chorea. *Personal History:*—He has frequently had "sore throat;" he had acute rheumatic fever with cardiac disease in 1905. *Present Illness:*—In October, 1907, he began to have cough and dyspnœa, which became worse so that he had to stop work in the latter part of November, '07. About Dec. 25th, '07, he began to have epigastric pain, anorexia and vomiting, which continued until his entrance to the Hospital on Dec. 30th, 1907. *Physical Examination on Entrance:*—The patient is a well developed young man with dyspnœa, orthopnœa and cyanosis, the pericardium bulges and exhibits a diffuse pulsation. The heart is enlarged to the left and right. There is a long murmur occupying the entire systole, it is heard best at the apex and is transmitted to the back. The second pulmonic sound is short and sharp. A faint presystolic thrill is present. There is passive congestion of both lungs. The liver is tender and extends 6 cm. below the costal border. Some ascites is present. Slight œdema is found over the shins. The temperature is 98° F., the pulse 108 and the respiration 30.

Jan. 4. Jaundice present.

Jan. 6. Heart and liver are slightly smaller. Temperature, 101.5° F.

Jan. 11. There is a to-and-fro friction sound over the pericardium. Temperature 102° F.

Jan. 12. There are signs of fluid in the pericardium. Temperature 101.5° F.

Jan. 13. The cardiac dullness steadily increases and the friction rub is less apparent.

Jan. 14. Paracentesis of pericardium is unsuccessful.

Jan. 15. There is swelling of the left arm and there are signs of consolidation of the apex of the lower lobe of the left lung.

Jan. 20. Cardiac dullness has diminished and the patient is improving; the signs of consolidation in left lung are much less but there are signs of fluid over the left apex. Temperature 100° to 102.5°.

Jan. 23. Erysipelas of the face has developed. Temperature, 104°.

Jan. 25. The condition has remained about the same until this morning when the patient died rather suddenly. Temperature, 103°.

An autopsy was performed seven hours post mortem and the anatomical diagnosis was as follows:

Facial erysipelas, Acute vegetative aortic endocarditis, Acute vegetative mitral endocarditis, Acute vegetative tricuspid endocarditis, Chronic mitral endocarditis, Acute serofibrinous pericarditis, Acute fibrinous pleuritis of right side, Acute serous apical pleuritis of the left side and Thrombosis of the left subclavian vein.

The bacteriological findings were as follows:

Smears from the aortic, mitral and tricuspid valves, the thrombus of the subclavian vein and the pericardium, gave streptococci.

Cultures from

Spleen,	B. Coli.
Liver,	Sterile.
Heart blood,	Sterile.
Thrombus,	Streptococcus.
Erysipelas,	Streptococcus and Staphylococcus albus
Pericardium,	Streptococcus.

A comparative study of the three strains of streptococci isolated showed them to be identical as far as staining and cultural methods could determine, They all gave a precipitate of bile salts and an acid reaction in McConkey's bile salt lactose broth, to which reference shall be made later.

There is little doubt that the cardiac lesions in this case were of rheumatic origin and it is probable that the erysipelas was caused by the same organism. In this case, at least, we may conclude that erysipelas has been caused by the same organism that produces acute rheumatic fever.

The exhaustive studies carried out by Marmorek on different strains of streptococci have led him to believe that they are all identical or at least cannot be differentiated. He basis this belief on the fact that none of these streptococci will grow in the filtrate obtained by filtering broth in which one strain of streptococcus has been grown. Gordon[12] has recently advocated for their differentiation the use of a very elaborate series of culture media. The principle on which he bases his work, is, that there may be different chemical reactions with the growth of each class. Gordon and Houston examined about 800 different strains. Later Andrews and Horter[13] made a very elaborate study of about 400 more colonies. They combine these results with those of Gordon and Houston and attempt to classify 1200 strains by means of the reactions obtained on Gordon's series of media. They find the following classes.

1. Streptococcus equinis.
2. Streptococcus mitis.
3. Streptococcus pyogenes.
4. Streptococcus salivarius.
5. Streptococcus anginosus.
6. Streptococcus fæcalis.
7. Pneumococcus.

Besides these classes they have made numerous sub-divisions which depend upon differences of minor importance. They acknowledge that the classification is complicated but hope that more study may simplify it and make it more practicable.

Among 400 organisms examined by Andrews and Horter there were six which might be called Streptococcus rheumaticus because they had been obtained from cases of rheumatism. They isolated four strains from cases of acute rheumatic fever examined at autopsy; one was obtained from Payne and one from Beattie. These six strains were classified as follows:

1. Streptococcus pyogenes.
1. Streptococcus salivarius (Payne).
1. Streptococcus fæcalis (Beattie).
3. Streptococcus anginosus.

In order to compare Streptococcus rheumaticus with other streptococci by the method of Gordon, I have examined nine strains of streptococci from various sources with the following results:

1 organism from chronic arthritis is classified as anginosus.
1 organism from blood of acute rheumatic fever is classified as anginosus.
1 organism from tonsillar crypt is classified as anginosus.
3 organisms from tonsillar crypts are classified as fæcalis.
1 organism from cellulitis is classified as pyogenes.

Streptococcus rheumaticus, which has been obtained from Dr. Cole, of Baltimore, and is a transfer from one of Payne's original strains, is classified as pyogenes.

1 organism from erysipelas in the case reported above is classified as salivarius.

1 organism from pericardium in the case reported above is classified as salivarius.

1 organism from thrombi in the case reported above is classified as salivarius.

The last three organisms will be considered as one strain, since no differences have been found.

Eight distinct strains of the so-called Streptococcus rheumaticus have been examined by the method of Gordon and the results are much at variance:

2 strains appear to be streptococcus pyogenes.
2 strains appear to be streptococcus salivarius.
1 strain appears to be streptococcus fæcalis.
3 strains appear to be streptococcus anginosus.

According to this classification Streptococcus rheumaticus is not a distinct organism separate from other streptococci.

Beatty[14] of Edinburgh, who reports an extensive bacteriological study of so-called Streptococcus rheumaticus, states that the only peculiarities of this organism which, as far as he has been able to demonstrate, distinguish it from other strains of streptococci, are the following:

1. The acidulation and deposit of bile salts in McConkey's bile salt lactose broth.

2. The formation of a serous exudate in the synovial membranes, while other strains of streptococci produced a purulent exudate.

In order to test the value of these two points of differentiation I have performed the following experiments:

Twenty-five strains of streptococci from different individuals and different sources were examined to determine their action in McConkey's bile salt lactose broth. They were the following:

1 organism from a chronic arthritis.
1 organism from the blood of acute rheumatic fever.
4 organisms from tonsillar crypts.
14 organisms from the interior of tonsils after extirpation.
2 organisms from cellulitis.
1 organism from an empyemic sinus.
1 Streptococcus rheumaticus from Dr. Payne.
1 organism from rheumatic pericarditis.

Of these organisms, eight produced an acid reaction and deposited bile salts after an incubation period of seventy-two hours. They were the following:

1 organism from chronic arthritis.
1 organism from the blood of acute rheumatic fever.
3 organisms from the interior of tonsils after extirpation.
2 organisms from cellulitis.
1 Streptococcus rheumaticus. (Payne).

It may be well, first, to draw attention to the fact that two strains, perhaps three, of so-called Streptococcus rheumaticus gave the reaction just mentioned. On the other hand, five other strains also gave it. It is possible that the three organisms obtained from the tonsils were also Streptococcus rheumaticus, as they were obtained from patients with acute rheumatic fever. But the other two organisms were isolated from very severe cases of cellulitis with no manifestations of acute rheumatic fever. The streptococcus from a case of rheumatic pericarditis, on the contrary, did not give the reaction. It cannot be said that this reaction is peculiar to any variety of streptococci.

That so-called Streptococcus rheumaticus is the only streptococcus which produces a serous exudate in the serous cavities has repeatedly been shown to be false[17]. The following experiments confirm many similar experiments already reported and they demonstrate several facts of interest:

Thirteen rabbits were inoculated in the ear vein with streptococci suspended in normal saline solution. Nine different strains which were employed, were obtained as follows:

1. Chronic arthritis.
2. Blood of acute rheumatic fever.
3. Interior of tonsil after operation (from a case of acute rheumatic fever).
4. Interior of tonsil after operation (from a case of acute rheumatic fever).
5. Interior of tonsil after operation (from a case of acute rheumatic fever).
6. Cellulitis.
7. Abscess.
8. Empyema.
9. Streptococcus rheumaticus from Dr. Payne.

Rabbit 1.—Growth from one agar slant of streptococcus "K," obtained from the knee of a case of chronic arthritis, was injected into the ear vein on Feb. 10, '07.

Feb. 11. Animal shows slight limping of right foreleg; examination is negative. It has increased motor excitability.

Feb. 12. There are fine fibrillary twitchings of the muscles, which increase with excitement. There are swelling and redness of the right wrist and elbow. At 5 P. M. the animal has general epileptiform convulsions and tetanic spasms lasting several hours On the next day the right foreleg remained unchanged but the animal used the hind legs with difficulty and it has much difficulty in walking.

Feb. 16. The animal is normal.

Repeated injections of streptococci into the ear vein produced a fugacious arthritis lasting a few days, but the animal always recovered.

Rabbit 2.—Dec. 10, '06. Growth from four cultures on agar of streptococcus "G," obtained from the blood of a case of acute rheumatic fever, was suspended in salt solution and injected into the ear vein.

Dec. 11. There is marked limping of the hind legs with swelling of both knees.

Dec. 24. The animal has had every joint in the extremities involved for a few days at a time and there has been swelling and redness of nearly all of them.

Dec. 31. The joints are normal.

Repeated injections of streptococci produced an effect just described. On Jan. 25, '07, the joints are normal but the animal seems very sick.

Jan. 26. The animal died. Autopsy shows no lesion. Cultures are sterile.

Rabbit 3.—January 24, '07. Growth from three agar slant cultures of streptococcus "H," obtained from the interior of the tonsils after extirpation from a case of acute rheumatic fever, was injected intravenously.

Jan. 25. There is arthritis of right foreleg with swelling and tenderness of right elbow.

Jan. 31. Extremities are normal.

The animal was not again injected but on March 28, '07, a slight limp of the right hind leg was noted. This continued and gradually became more marked. On April 15, '07, there was a definite firm enlargement of the joint with atrophy of the tissues above and below. On May 27 the swelling had increased. It seemed due to bony and capsular change and there was no sign of effusion. The muscles were much atrophied. On May 30 a skiagraph was taken and it showed distinct exostoses.

On June 20, '07, the animal died suddenly.

The cause of death was found to be torsion of the right cornu of a pregnant uterus. Other viscera were normal. The right knee was distinctly larger than the left and there was thickening of the periarticular tissue. On opening the joint a small quantity of thick, tenacious. non-purulent fluid escaped. There was some thickening of the villi and the cartilages had lost their lustre. There was slight erosion along the cartilagenous edges and also some hypertrophy of the cartilage. Cultures were negative

One of the villi was incubated in bouillon but no bacteria grew.

RABBIT 4.—The growth from one agar slant culture of streptococcus "S," obtained from the interior of the tonsils from a case of acute rheumatic fever, was injected into the ear vein on Nov. 21, '06. No arthritis developed. The animal was again injected on Nov. 24, '06, with the growth from two slant cultures. There was still no effect. The growth from three tubes was injected on Dec. 3, '06, and on Dec. 9 marked lameness of the fore legs with swelling and tenderness of the elbows and shoulders developed. This condition persisted until Dec. 14, and ten days later the growth from six agar slants was injected. Slight lameness of the left hind leg developed but soon disappeared. For two days the animal appeared in normal condition, but on Dec. 30 it suddenly developed complete paraplegia and the animal became semi-conscious. The next day the animal had numerous epileptiform convulsions, followed by death.

At autopsy all the viscera were found normal except the central nervous system. There were extensive hemorrhages in the dorsal and cervical cord, in the meninges of the cord and in the meninges over the medulla, cerebellum and base of the brain. No areas of softening were found.

Cultures and smear preparations from the central nervous system, cerebrospinal fluid, viscera, blood, joints and synovial membranes showed no organisms.

RABBIT 5.—The animal was repeatedly injected with the streptococcus "Gr," obtained from the interior of the tonsils of a case of acute rheumatic fever, but it was not until the growth from seven agar slants were given that the animal showed ill effects. A fleeting arthritis of all the joints developed, lasted a few days and quickly disappeared.

RABBIT 6.—On May 4, '07, the animal was injected with the growth from two agar slant cultures of streptococcus designated "cellulitis." On May 6, arthritis of the left hind leg developed, lasting three days, and completely disappeared.

RABBIT 7.—On Dec. 6, '07, the growth from one agar slant culture of streptococcus designated "abscess" was injected intravenously. There was no effect. This injection was repeated on Dec. 17, and again on Dec. 25. Two days later severe arthritis of the left knee joint with tenderness and swelling developed. Arthritis persisted for five days and quickly subsided.

RABBIT 8.—The growth from one agar slant culture of streptococcus designated "empyema" was injected on Dec. 6, '07. Arthritis of the left fore leg developed two days later and quickly disappeared. On Dec. 26, the injection was repeated. Two days later the right fore leg was affected. This inflammation soon improved but the ankle of the right hind leg showed swelling and tenderness. On Jan. 7, '08, the animal was again normal.

RABBIT 9.—The animal was repeatedly injected with Streptococcus rheumaticus but did not develope arthritis. It became very ill and died two weeks after the last injection. It had received at different times the growth from eighteen agar slant cultures. The post-mortem findings were as follows: Miliary abscesses of the kidneys; acute vegetative, mitral and aortic endocarditis. The joints were normal.

Cultures from the peritoneum remained sterile. Cultures from the liver contained B. Coli and streptococci, and from spleen, heart blood and kidney abscesses streptococci. Smears from aortic and mitral valves and from the abscess of the kidney contained streptococci.

RABBIT 10.—This animal was repeatedly injected intravenously with Streptococcus rheumaticus after the organisms had been passed through five mice. On one occasion it was given the growth from sixteen agar slant cultures but no untoward results followed.

RABBIT 11.—The same result followed in this case as in the preceding one, even after very large doses of Streptococcus rheumaticus.

RABBIT 12.—The Streptococcus rheumaticus isolated from the heart blood of Rabbit 9 was injected in this case but without effect.

RABBIT 13.—This animal was treated in the same way as Rabbit 11 and there was a similar result.

It will be seen from this short review of the animals used that streptococcus does not always cause arthritis or produce a purulent exudate into the joints. In eight animals in which various strains were used a fugacious non-purulent arthritis ensued. It is also just to point out that three of these organisms also gave a positive reaction in McConkey's bile salt lactose broth. But with the other five organisms, which failed to give this cultural reaction, an acute arthritis also developed.

The results obtained by the injection of Streptococcus rheumaticus are disappointing. Among the six animals with blood infection only one Rabbit, No. 2, developed joint lesions. One Rabbit, No. 5, died as the result of acute endocarditis and general streptococcæmia. The areas in the kidneys might have been infarcts but they had the appearance of miliary abscesses, but no histological examinations were made, so abscess formation was not established with certainty. It is noteworthy, nevertheless, that this was the only organism which has apparently produced a purulent process.

Several facts of interest shown by this series of experiments may be noted. In Rabbit No. 1, forty-eight hours after the original injections and synchronous with arthritic lesions, there was very marked hyperæsthesia with general convulsions which lasted several hours. After this time the animal remained very excitable with marked twitching of the extremities for several days, but eventually recovered.

In Rabbit No. 4 there was a somewhat similar clinical picture but the result was different. At autopsy hemorrhages into the substance of the cervical and dorsal cord with many hemorrhages in the meninges were found. The resemblance between these two cases is well marked but its interpretation is problematical; it is mentioned because there is perhaps an etiological relationship between chorea and acute rheumatic fever. Poynton and Paine have reported a doubtful instance of choreiform movements in a rabbit after intravenous injections of streptococcus.

These experiments seem to corroborate the findings of previous workers, namely, that acute rheumatic fever is a streptococcus infection. That there is a separate and distinct strain of streptococcus which causes this disease has not been proven and the results described are strong evidence to the contrary.

The power of the sera of patients to agglutinate streptococci has been repeatedly investigated, but this property has not been demonstrated. The opsonic activity of the blood at first offered hope of a trustworthy means for testing the peculiarities of streptococci from different sources.. With this object in view I determined the opsonic index of the blood of twenty patients suffering from acute rheumatic fever. A variety of organisms were used, including "streptococcus rheumaticus," streptococcus from the tonsils of each patient, gonococcus and staphylococcus aureus. The results were unsatisfactory. There was great variation of the opsonic index, determined at different times, and when the index remained constant it exhibited no peculiar relation to any micro-organism.

After the etiology of an infectious disease has been determined effort is naturally made to find the point of entry. It cannot be doubted that many cases of acute rheumatic fever occur without any prodromata. The point of entry may not be always the same. For many years the close relationship between acute follicular tonsillitis, so-called angina, and acute rheumatic fever has been recognized. Lemoine[15] reported the finding of streptococcus in pure culture in the interior of the tonsils in 165 cases of tonsillitis associated with acute rheumatic fever.

With the object of determining, if possible, the frequency of streptococci in the tonsils of rheumatic patients, the following experiments were performed: In thirteen cases of acute rheumatic fever in the wards of the Johns Hopkins Hospital the tonsils were enucleated and in every case removed without tearing. Cultures were immediately taken from the crypts or external surface and inoculated on glycerine agar. The object of these cultures was to determine, for comparison, the flora of the pharynx. The tonsils were then opened with aseptic precautions and the cut surface seared with a hot iron. A stab opening was made into the substance and cultures obtained on glycerine agar and agar plates. The entire tonsil was washed in a solution of bichloride of mercury, of strength 1 to 1000, for thirty seconds, and thoroughly rinsed in sterile normal saline solution contained in several dishes. The entire tonsil was placed in flasks of bouillon or of litmus-milk. After incubation for forty-eight hours agar plates and smears were made from the growth in the flasks.

The culture from the surface of the tonsil showed in every case growth of a variety of organisms, but in every instance streptococci were found. The cultures from the interior of the tonsil taken through the sterile surface revealed a great diminution in the number and variety of organisms. Of eleven cases so examined there was a pure culture of streptococci in eight (73 per cent.). In the other three cases a few staphylococci were twice associated with streptococci and an unknown bacillus once accompanied streptococci. The tonsils were incubated *en masse* in ten cases and in nine (90 per cent.) a pure culture of streptococcus was obtained. In the other case streptococcus was associated with staphylococcus aureus. In eleven of the twelve cases examined a pure culture of streptococcus was obtained either by puncture of the surface sterilized by heat or by incubation *en masse*.

It is noteworthy that both tonsils have yielded similar results in almost all cases. Moreover, the great variety of organisms obtained from the external cultures and the uniformity of the finding of streptococcus in the interior and autolysed cultures are significant. A cultural study of these strains did not show material differences. Three gave acidulation and deposit of bile salts in McConkey's bile salt lactose broth, while the others failed to produce this reaction.

The observations just described show that streptococci may be present in the interior of the tonsil without giving any external signs of disease. Pharyngitis is frequently observed with acute rheumatic fever and is associated with enlargement of the lymphatic glands draining the inflamed area. It is well known that lymphatics carry lymph from the tonsils through the cervical glands to the thoracic duct. The foregoing observations suggest that streptococci may be dormant in the tonsils. The reinfection so common in acute rheumatic fever may be explained by this fact.

The tonsils and pharynx may not be the only portals of infection. Since tubercle bacilli may pass through an apparently normal intestinal mucosa, it is not impossible that streptococci may enter in the same way. Chvostek[16] believes that the tonsil and the intestinal tract are the portals of entry for the streptococcus in acute rheumatic fever.

Conclusions.

1. Acute rheumatic fever is the result of infection with streptococcus.
2. The disease at some stage is a streptococcæmia.
3. The streptococcus producing acute rheumatic fever is indistinguishable morphologically, culturally and biologically from other streptococci.
4. The tonsil is probably an important portal of entry for the streptococcus in acute rheumatic fever.

This work was commenced in the Biological Laboratory of the Medical Clinic of Johns Hopkins University, Baltimore, and completed in the Pathological Laboratory of the Presbyterian Hospital of New York City.

I wish to express my thanks to Dr. Barker and Dr. Cole for their valuable aid and advice in this work and to Dr. Rosenheim for the tonsils obtained by operation.

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X.

A STUDY OF THE PATHOLOGICAL ANATOMY OF THE PANCREAS IN NINETY CASES OF DIABETES MELLITUS.

By Russell L. Cecil, M.D., Externe Pathologist.

Study of anatomical changes in diabetes mellitus has been limited almost exclusively to lesions which occur in the pancreas. As far back as 1788, Thomas Cawley[1] described sclerosis of the pancreas and pancreatic calculi in connection with diabetes. In 1877, Lancereaux[2] noted lesions in the pancreas which he believed were constantly present in cases of severe diabetes with emaciation.

Langerhans[3] was the first to describe carefully the histology of the normal pancreas. He called attention to small oval groups of cells which are situated between the acini and differ from the acinar cells in size, arrangement and staining qualities. These bodies have since come to be known as islands of Langerhans.

In 1889, were published the well-known experiments of von Mering and Minkowski,[4] in which they showed that removal of the pancreas in dogs produced typical diabetes. It has been found, however, that glycosuria and the other symptoms of diabetes fail to appear if as much as a fourth or a fifth of the pancreas be allowed to remain. The diabetes of depancreatized dogs has suggested that the pancreas furnishes an internal secretion which controls carbohydrate metabolism. Since the other organs of internal secretion are ductless glands, the islands of Langerhans, the only parenchymatous tissue in the pancreas not in communication with the ducts, were associated with pancreatic internal secretion at a time when evidence of this association was wanting. Laguesse[5] and Schäfer[6] were the first to suggest that these bodies might be concerned in the production of an internal secretion which played an important part in the metabolism of sugar.

Oser,[7] in 1898, collected one hundred and eighty-eight cases of diabetes in which the pancreas exhibited lesions. He classified the lesions as follows:

Atrophy	78
Fatty Change (lipomatosis in all but 2)	10
Induration	22
Calculi	24
Carcinoma	24
Cyst	9
Abscess	6
Hemorrhage	3
Necrosis	3
Fat Necrosis	2
Lesions recognizable only by microscope	7

This classification of Oser was based upon macroscopic changes, for the lesions recognizable chiefly by the microscope, such as chronic inflammation, form a very small percentage of his cases.

Opie,[8] in 1900, described definite pathological changes in the islands of Langerhans in diabetes. These changes consisted most frequently in increase of fibrous tissue within and about the islands. In other cases of diabetes Opie found hyaline degeneration of the islands of Langerhans, occasionally, too, in a pancreas otherwise entirely normal. Opie reached the conclusion that where diabetes is caused by a lesion of the pancreas, the lesion is of such a character as to injure or destroy the islands of Langerhans. Opie's studies have been followed by a large number of articles upon the same subject, and some observers have supported while others have opposed his views. In addition to the lesions described by Opie, other changes in the islands of Langerhans have been noted in association with diabetes mellitus. Schmidt[9] found acute inflammation limited to the interacinar islands in a child ten years old. Ssobolew,[10] Herzog,[11] Weichselbaum and Stangl,[12] and Opie[23] have reported absence of the islands of Langerhans, or great diminution in their number. Hypertrophy of these islands, associated with a peculiar adenoma-like arrangement of their cells, has been described by Reitmann,[13] Herxheimer,[14] McCallum[15] and others.

Sauerbeck,[16] in 1902, collected from various sources one hundred and seventy-six cases of diabetes in which the condition of the islands had been noted. He found that lesions in the islands of Langerhans had been observed in sixty-two per cent. of the cases. Weichselbaum and Stangl[12] studied the islands in thirty-four cases of diabetes and found qualitative or quantitative changes in all but two cases. Hansemann,[17] after investigating thirty-four cases, is convinced that no relationship exists between the interacinar islands and diabetes.

The present work was undertaken at the suggestion of Dr. Opie, with the hope that the study of a large number of cases by a single observer might furnish accurate information concerning the condition of the pancreas and of the islands of Langerhans in diabetes mellitus. So far as I know, only two of the following cases have been previously reported. The cases have not been selected with any regard to the condition of the pancreas, or to the type of diabetes. Altogether, pancreatic tissue from ninety cases has been collected from various hospitals and physicians in this country and in Canada. I have been able to obtain clinical data in connection with most of these cases. The age of individuals affected with the disease has varied from ten to seventy-five years. In the largest number of cases the disease has occurred between the fiftieth and sixtieth year, whereas the age in twenty-four of the cases has been under thirty years of age.

GROSS PATHOLOGY OF THE PANCREAS IN DIABETES.

Although macroscopic lesions of the pancreas, such as cancer, cysts, calculi, hemorrhagic inflammation and lipomatosis, are comparatively common, it is only in exceptional cases that they are accompanied by diabetes. When, with calculi, cyst or cancer occluding the pancreatic duct, or with chronic inflammation having its origin in the ducts of the gland, diabetes is present, an advanced fibrosis is generally found associated with the primary lesion and is characterized by broad bands of connective tissue between the lobules of the glands. Opie[8] has described an interacinar type of chronic interstitial inflammation which consists of a delicate new growth of fibrous tissue between the glandular acini. He found this lesion present in seventy-five per cent. of all cases of diabetes. On the other hand, in twenty-one cases of chronic interstitial inflammation, in which the sclerosis was primarily interlobular, diabetes occurred only once, and in this case, there was advanced destruction of parenchyma.

Opie believes that the simple or "granular" atrophy of the pancreas, which certain writers, including Hansemann, consider a common lesion in diabetes, differs in no way from the chronic interacinar inflammation which he and others have noted.

Of my cases, the pancreas has been described as small or atrophic in only twenty-five percent. All but four of these showed a definite interacinar pancreatitis. These four cases occurred in the second and third decades of life. With the exception of this diminution in size, the pancreas in my cases exhibited very few notable macroscopic changes. The weight has been given in thirty-five cases, and ranges from thirty to one hundred and eighty-five grammes. The average weight was ninety-four grammes. This is scarcely less than the weight of the average normal pancreas, which ranges from sixty-six to one hundred and two grammes, and averages, according to Vierordt, ninety-seven grammes. The consistence of the gland in a good many cases was

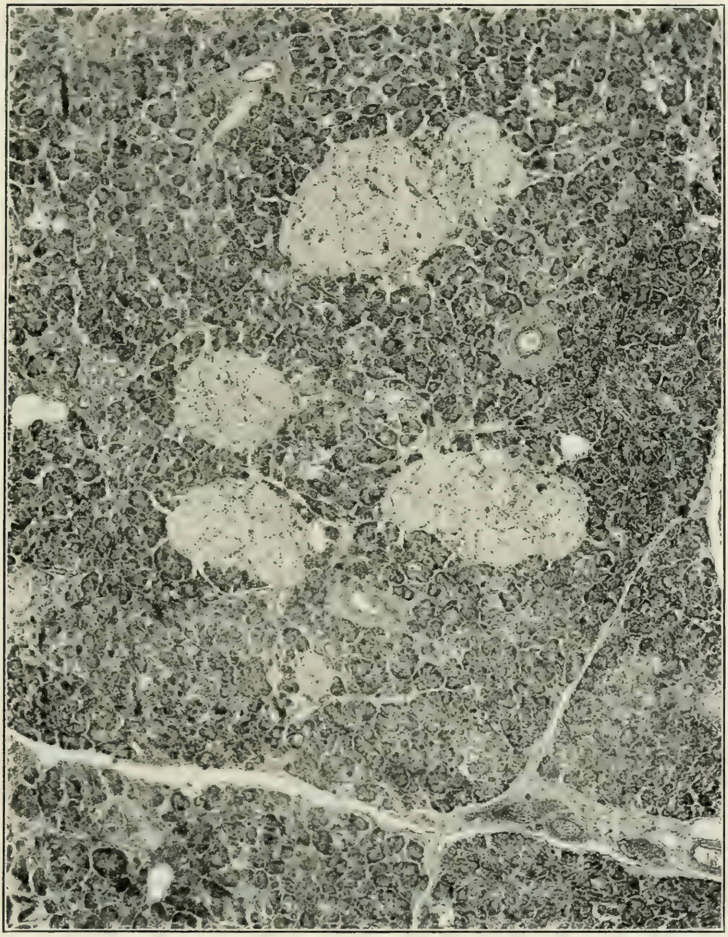

FIG. 1—HYALINE DEGENERATION OF THE ISLANDS OF LANGERHANS: SECRETING PARENCHYMA NORMAL (CASE LXXI)

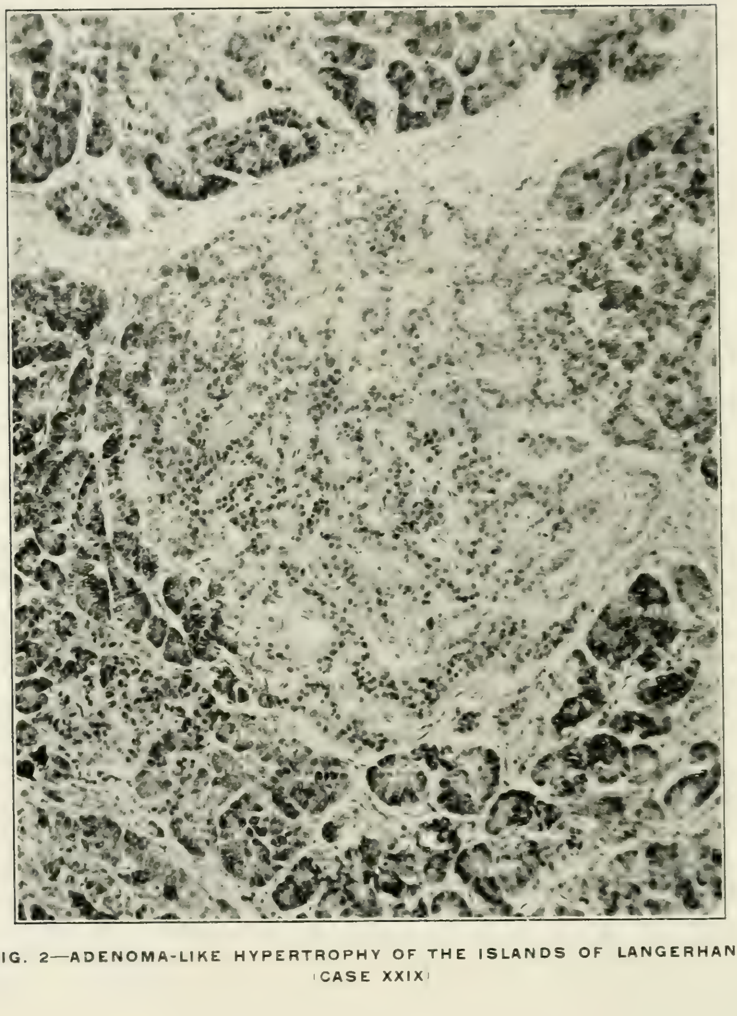

FIG. 2—ADENOMA-LIKE HYPERTROPHY OF THE ISLANDS OF LANGERHANS
(CASE XXIX)

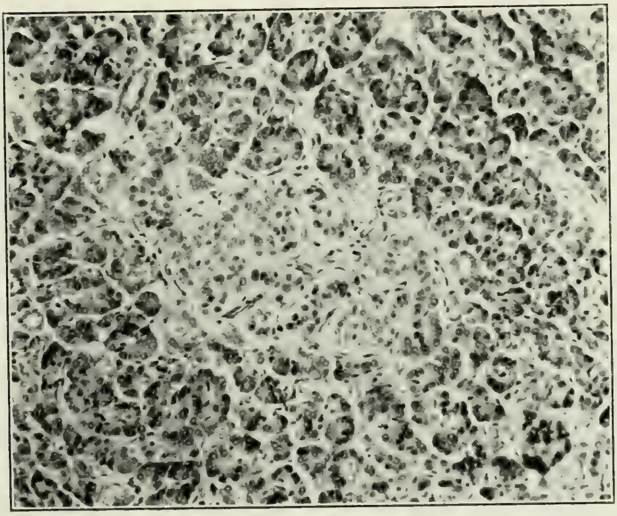

FIG. 3—SCLEROSIS OF ISLAND OF LANGERHANS. NORMAL SECRETING PARENCHYMA (CASE XXXVIII)

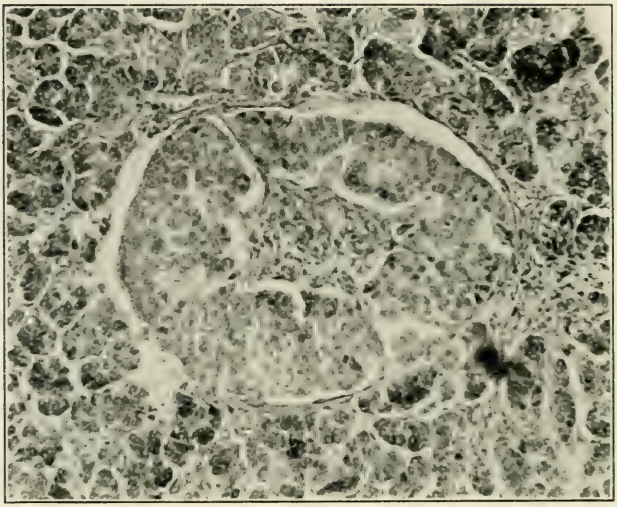

FIG. 4—SCLEROSIS OF ISLAND OF LANGERHANS (CASE LXI)

increased. The lobulation was indistinct in some instances and in fifteen an infiltration of fat tissue was visible with the naked eye. Neither cancer, cysts nor calculi of the pancreas were encountered. There were no cases of pancreatic apoplexy.

Microscopic Changes in the Pancreas.

In considering the histological pathology of the pancreas in diabetes, it will be convenient to divide the subject into three parts:

(1) Changes in the interstitial tissue.
(2) Changes in the glandular acini.
(3) Changes in the islands of Langerhans.

Changes in the Interstitial Tissue.—Chronic inflammation of the pancreas is a process which is not confined to diabetes. Birch-Hirschfeld,[19] Schlesinger,[20] Opie and others have described chronic interstitial pancreatitis encountered in cases of congenital syphilis. Occlusion of the pancreatic ducts by calculi, new growths, or ligation, produces in many instances a very severe form of chronic interstitial inflammation. Shulze[21] ligated the pancreas in guinea-pigs and found that the portion of the gland distal to the ligature underwent a marked sclerosis; the secreting parenchyma atrophied, while the islands of Langerhans persisted unchanged in the newly formed stroma. Ssobolew[10] obtained similar results. Opie[8] has shown that the interstitial changes which follow obstruction of the duct differ from those observed in connection with diabetes. In the former, sclerosis is chiefly interlobular, and while the lobules may be invaded to a greater or less extent by the newly formed tissue, the progress of the lesion is apparently inward from the periphery of the lobule. In the pancreatitis of diabetes the reverse is true. The new growth originates between the acini, and interlobular sclerosis, if present at all, is a later phase of the process.

Of the ninety cases which I have studied, sixty-four, that is, seventy-one per cent., show a definite chronic interacinar pancreatitis. In twenty-one, or twenty-four per cent., the sclerosis is marked. The distribution of this new growth is generally uneven, some lobules being more involved than others. In a number of cases this "focal" sclerosis is conspicuous. Where the induration is advanced, many of the lobules have been largely replaced by fibrous tissue, while the glandular acini which still survive are compressed and distorted, and may give evidence of atrophy. Although the new-formed fibrous tissue is often most conspicuous about the vessels and ducts, I have not been able to establish any constant relationship. In many cases, especially where the lesion is mild, the sclerosis seems more advanced in the neighborhood of the islands of Langerhans.

The relation of age to chronic interacinar inflammation is important. The lesion has been entirely absent in all of the four cases under twenty years of age. Between the ages of twenty and thirty, only twenty-five per cent. of cases show interacinar new growth. After thirty, interacinar sclerosis is the rule, being present in ninety per cent. of all cases.

Typical chronic inflammation of the interlobular variety has been observed in only four cases. A well-marked interacinar invasion was present in all four cases. A slight and very irregularly distributed interlobular fibrosis is seen in some severer instances of chronic interacinar inflammation, but here the process appears to be a local extension of the changes between the acini. Of the four cases just mentioned, one was associated with a duodenal ulcer, one with persistent vomiting, and another with diphtheritic colitis. In the remaining case, no history was obtained. The associated intestinal lesion suggests ascending infection of the pancreatic duct.

The newly formed connective tissue, which is seen in both types of chronic interstitial pancreatitis, is generally of a dense fibrous character and rather poor in spindle cells. In a number of my cases, however, the new growth is of a looser texture and quite cellular, resembling the stroma of an infant's pancreas. The density probably increases with the duration of the inflammation, though I have not been able to verify this suggestion by a study of these cases.

An extensive infiltration of lymphoid, eosinophile and plasma cells has been observed very frequently with both types of chronic interstitial pancreatitis. The stroma of a normal pancreas often contains a moderate number of such cells, but this fact does not account for the great number frequently encountered in chronic interstitial inflammation. Of the sixty-four cases with interacinar pancreatitis, thirty have shown an abundant cellular infiltration. Lymphoid cells constitute the greater part of this infiltration, but eosinophile cells and plasma cells are also plentiful. The presence of a considerable number of cellular elements in the stroma would seem to indicate that the inflammatory process was still in the active stage. In my cases, however, no relationship could be established between this type of infiltration and the duration or severity of the diabetes. A marked infiltration of lymphoid cells was present in each of the four cases of chronic interlobular pancreatitis. Polymorphonuclear leucocytes were found in the stroma in greater or less numbers in twelve cases, always associated with infiltration of lymphoid cells. The presence of the former naturally suggests an acute process, and this relationship is apparently confirmed by our cases. In the six cases of this group, where clinical data have been at hand, the duration of the diabetes in all but one has been less than a year. In this one (Case LXVI), the leucocytes were confined to the immediate neighborhood of the ducts, which appear to be the sites of a suppurative inflammation.

A few miliary tubercles were found in the stroma of the pancreas in Case XXII.

Considerable infiltration of the pancreatic stroma by adipose tissue was found in twenty-six of my cases. Three of these showed a very marked invasion, the lobules as well as many of the acini being widely separated by fatty tissue. In these three cases the parenchyma appeared much reduced in amount and the sections gave the impression that many acini had been replaced by adipose tissue. The islands of Langerhans were very scarce in one case (Case XXXVI). In the other two (Cases L and LXXVIII), a considerable number of interacinar islands were found. One of these cases of pancreatic lipomatosis was associated with obesity.

A marked pancreatic lipomatosis, unaccompanied by diabetes, was encountered recently in a case which came to autopsy at the Presbyterian Hospital. Only a very small fraction of the parenchyma survived; this was exceedingly rich in islands of Langerhans, which were well preserved and had evidently resisted the invasion of fatty tissue more successfully than the glandular acini.

Arteriosclerosis, it is well known, accompanies a large percentage of cases of diabetes. Of my cases, eighty per cent. showed a thickening of the wall of the pancreatic vessels, and in half of these cases the vessels were also hyaline. The small arterioles seem to show this change first, and in many instances the lumen of the smaller vessel has been almost entirely obliterated by hyperplasia of the medial coat. Hyaline changes were, moreover, more commonly observed in the small than in the large vessels.

The incidence of arteriosclerosis in diabetes increases rapidly with age, and in my series it was present in only twenty per cent. of the cases between twenty and thirty years of age, increased to eighty per cent. in cases between thirty and forty, and was present in all cases occurring after the fortieth year.

Changes in the Parenchyma.—Clinically and experimentally, cases are constantly encountered which give no evidence of a disturbance in carbohydrate metabolism, although they show at autopsy extensive destruction of the glandular acini. Arnozan and Vaillard[22] have shown that with partial or complete occlusion of the pancreatic ducts, the glandular acini undergo a rapid and wide-spread dissolution, and their places are taken by connective tissue. Ascending infection or irritants from the intestines may produce chronic inflammation of the pancreas, and more or less destruction of glandular tissue. According to my observations, the most common change of the acini with diabetes is compression and atrophy, seen in association with the severer types of chronic interacinar pancreatitis. An acinus which has undergone this change is smaller than the normal; its constituent cells are pressed together and individual cells are ill defined; in some acini a number of the cells have already been destroyed, so that only a part of the original acinus remains. Many acini have been completely obliterated and their place is taken by connective tissue. In striking contrast to the atrophied acini and occasionally associated with them in the same section are acini which are larger than the normal, rich in centro-acinar cells, and suggestive of a compensatory hypertrophy.

The brightly staining eosinophile acini first described by Opie,[23] have been observed in nine of my cases. Such an acinus or group of acini, takes a bright pink stain in preparations stained with hæmatoxylin and eosin, and is sharply defined from the surrounding alveoli, appearing at first glance to be an island of Langerhans. There are, however, well-marked differences between the two. The cells of the former are larger than the island cells, columnar in shape, and arranged in the form of definite acini. No conclusive explanation of this change has been offered, and examination of these nine cases gives no additional information. The view that they are exhausted acini is probably the most plausible explanation of their occurrence.

Changes in the Islands of Langerhans.—The interacinar island of a normal pancreas presents a characteristic picture. It is composed of irregularly polygonal cells, smaller than the alveolar cells, with homogeneous, faintly staining cell bodies and large round nuclei rich in chromatin. The cells are grouped in branching and anastomosing cords which exhibit no lumen nor suggestion of definite cellular arrangement. These cords of cells are separated from one another by large, irregular capillaries or "Sinusoids," which afford a rich vascular supply to the island. The sinusoids or capillaries have a very delicate wall formed by endothelial cells and are in intimate contact with the insular cells. Lydia Dewitt,[24] by employing Mallory's[18] stain, was able to demonstrate a thin capsule of connective tissue about the island, and delicate fibrillæ separating most of the island cells. According to Dewitt, the amount of connective tissue in the islands of Langerhans increases with age. In adults she found definite fibrillar trabeculæ following the courses of the larger sinusoids. By a process of digestion Flint[23] has shown that the fibrous reticulum of an interacinar island is coarser than the framework which supports the secreting acini. With the use of the hæmatoxylin and eosin stain, I have been unable, in the normal pancreas, to detect connective tissue between the individual cells of the islands, but the capsule and fibrous sheaths about the vessels are easily demonstrable.

In the ninety cases which I have studied, seventy-nine, or eighty-eight per cent., have shown definite anatomical changes in the islands. By far the commonest lesion was fibrosis, which was observed in seventy-six cases. In forty it was moderate; in thirty-five advanced. In the former cases the islands are surrounded by capsules of fibrous tissue which are thicker than the normal, almost invisible sheaths. The fibrillary coating of the insular capillaries is also definitely increased in thickness, converting the vessels into coarse septa, which extend in from the capsule and anastomose at the centre of the interacinar island. The cells forming the columns show little or no change in number or appearance. The following are the cases which show *moderate* sclerosis of the islands:

Cases V, X, XV, XIX, XXIV, XXV, XXXIII, XXXIV, XXXV, XXXVI, XXXVIII, XXXIX, XL, XLI, XLII, XLIV, XLVII, XLIX, L, LI, LII, LV, LVI, LIX, LX, LXIII, LXIV, LXVIII, LXIX, LXX, LXXV, LXXVI, LXXVII, LXXVIII, LXXXII, LXXXIII, LXXXVI, LXXXVII, LXXXVIII, XC, etc.

In the second group of cases the lesions are of a similar nature, but more advanced. The islands of Langerhans are imbedded in dense fibrous tissue which separates them from the surrounding alveoli. The intra-insular sclerosis still follows the path of the insular capillaries, the walls of which are several times thicker than the normal. Sections through the centre of the body will show an extensive patch of dense fibrous material, rich in spindle cells and sending out broad septa towards the periphery. The cells of the islands are often reduced in number, and appear small and compressed. Occasionally an island of Langerhans is found which has been almost completely converted into fibrous tissue (Cases IV, IX, XXVI, and LXXXI). The following are the cases which show *advanced* sclerosis of the islands:

Cases I, III, IV, VI, VIII, IX, XI, XII, XIV, XVI, XVII, XVIII, XX, XXI, XXII, XXVI, XXVIII, XXIX, XXXII, XXXVII, XLIII, XLV, XLVIII, LIII, LVIII, LXI, LXII, LXV, LXVII, LXXII, LXXIX, LXXX, LXXXI, LXXXIV, LXXXV.

Insular sclerosis of the mild type is usually associated with a moderate chronic interacinar pancreatitis, but this relation is not present in all cases. In four of my cases, where there was no evidence of an interstitial inflammation, a definite increase of connective tissue was found in the interacinar islands (Cases V, XXXV, XXXVIII, and LVI). In these four cases the age varied from twenty-six to seventy years. Advanced sclerosis of the islands of Langerhans was always associated with considerable interacinar sclerosis, and the insular lesion was always most severe in those areas where the induration was most marked.

The relationship between sclerosis of the islands of Langerhans and arteriosclerosis is of interest. Fibrous changes in the islands are, with few exceptions, associated with a sclerosis of the smaller pancreatic arterioles. Of my cases of insular sclerosis, all but five showed thickening of the vessel walls; these five cases occurred in the earlier decades of life. A moderate fibrosis of the islands was present in all, but arterial thickening was not recognizable. Sclerosis of the island in its early stages is probably a part of more or less generalized arteriosclerosis. It doubtless affects the capillaries of the islands of Langerhans or their afferent vessels and in this respect resembles beginning fibrous changes in the glomeruli of the kidney. When the process is advanced, chronic interacinar inflammation is always present and the entire interstitial framework of the island becomes involved in the new growth. The insular capillaries, however, still bear the brunt of the attack.

Hyaline degeneration of the islands of Langerhans is the lesion which occurs next in frequency to sclerosis, being present in twenty-seven cases (thirty per cent.). In most instances, it was associated with sclerosis of the pancreatic vessels and of the islands of Langerhans. There were, indeed, only two exceptions to this rule (Cases LXXI and LXXIV). In these two instances the vessels of the pancreas appeared about normal, and the insular capillaries showed no appreciable thickening. In Case LXXI, the islands were so completely destroyed that their histological structure was entirely lost. In seven cases, with hyaline changes in the interacinar islands, there was no increase in the interacinar connective tissue (Cases LXXI, LXXIV, XLIX, XL, LXXXVI, LIV, and LXIV). As a rule the majority of the islands of Langerhans were affected, but in a few cases only an occasional island showed the change. The hyaline material is first deposited along the capillaries of the island, separating the latter from the cells. As the process advances, it extends outward. Many of the cells are replaced by the hyaline substance, and those which still survive are often compressed and atrophic. Eventually, the entire area of the island may be occupied by homogeneous hyaline material. The nuclei of the endothelial cells appear to persist longest, but finally these too are destroyed. Even then, however, the lumen of the capillary may remain patent, and the circulation continue through the island, the red corpuscles being found in channels. In only one of my cases did the process appear to have extended into the surrounding parenchymatous tissue, and here only to a slight degree.

I have found hyaline degeneration of the islands of Langerhans in only two of the cases under thirty years of age. It appears to be most common after the fifth decade. In my cases I have found that this lesion was, with the exception of one case, always associated with diabetes of more than one year's duration. The average duration of the diabetes in fifteen cases with hyaline islands was three years and six months. The maximum percentage of glucose in the urine averaged about the same in cases with hyaline degeneration and in those with sclerosis of the interacinar islands. The average percentage of glucose in cases with normal islands was considerably higher than that in either of the other groups.

Average per cent. of glucose:

Eight cases with normal islands	6.9
Forty cases with sclerotic islands	3.4
Fourteen cases with hyaline islands	4.1

In nine cases, I have observed a well-marked infiltration of leucocytes about the islands of Langerhans. With one exception, a more or less general infiltration of the same character accompanied this lesion, but the cells were more numerous and concentrated in the vicinity of the interacinar islands. This one exception (Case XXIII) was the case of a young man twenty years of age, whose diabetes ran a rapidly fatal course (exact duration not known). Macroscopically the pancreas was atrophic. Microscopically the pancreas was normal in every respect save for the infiltration of lymphoid and polynuclear cells about the islands of Langerhans. The cells were generally arranged in the form of a halo about the island of Langerhans, just outside of the capsule, though in some cases the island itself was invaded. The average duration of the diabetes in the six cases of this group where the duration was definitely stated was only eleven months.

Hypertrophy of the Islands of Langerhans.—Laguesse[5] found that the islands of Langerhans in the normal pancreas of man varied from one hundred to four hundred microns in diameter. Islands of Langerhans exceeding four hundred microns were very rare. Lydia Dewitt[24] measured these bodies in the human pancreas, and found that they averaged .0153 c. mm. in volume. In her measurements the diameter never reached 400 microns. The pancreas in forty per cent. of my cases showed islands of Langerhans which equalled or exceeded 400 microns in diameter. Round or ovoid islands were selected and the long diameter was measured.

In Case XXVI, an island of Langerhans was found which measured sixteen hundred microns—a diameter about eight times that of normal. In the cases where giant islands were found, the average size of the interacinar islands was increased. Hyaline degeneration of the islands was associated with about a third of the cases with hypertrophy, and it was observed that hypertrophied islands, as a rule, were free from hyaline material, or contained it in only small amounts. In three cases, giant islands occurred in a pancreas which was otherwise entirely normal. Chauffard and Ravant[33] claim to have found swelling and increase of size in the islands of Langerhans without glycosuria in thirteen cases of typhoid fever, two of pneumonia and one of erysipelas. Trevor[34] found similar changes in the islands of Langerhans in pneumonia and endocarditis.

Reitmann,[13] Herxheimer,[14] MacCallum[15] and others have described a peculiar form of hypertrophy of the interacinar islands, which they have encountered in the pancreas of some cases of diabetes. The cells displayed, instead of their usual arrangement in irregular cords or masses, a definite columnar arrangement, and were often grouped together in circular cords about capillaries. In seven of our cases, a similar lesion has been observed. The islands of Langerhans are considerably larger than the normal, some of them reaching a diameter of seven or eight hundred microns. Their contour is quite irregular, loops and cords of columnar epithelial cells push their way out between the adjacent acini, and, but for differences in staining reaction, might possibly be mistaken for normal glandular structure. In one of our cases (Case XXIX) the picture is truly remarkable. The islands are very numerous, and exceedingly large and irregular in outline; their general appearance is somewhat suggestive of a neoplasm. Adenomata of the islands have been described by Nichols,[25] Helmholtz,[26] and Morse,[27] but the bodies which they described were macroscopic tumors. In the case just mentioned, the pancreas was normal in its gross appearance and all the islands shared in the hyperplasia. In six of these cases hypertrophy of the islands of Langerhans was associated with increase of fibrous tissue about the insular capillaries.

Number of Islands of Langerhans.—The number of islands of Langerhans in the normal pancreas varies considerably. According to Laguesse,[5] the average is somewhat less than one island to each square millimeter; Sauerbeck's[16] estimation is one island per square millimeter, Opie's[23] five-tenths, and Dewitt's[24] one and five-tenths to the square millimetre. In some of my cases, the number of interacinar islands has been large, but this apparent increase in number may have been due in many cases to increase in size of the islands, as the two phenomena were usually observed together.

Diminution in the number of islands of Langerhans was a much commoner finding. While there was no instance in my series of a pancreas entirely devoid of islands of Langerhans, there were a number of specimens in which they were exceedingly few.

Several writers have found an absence or scarcity of islands in diabetes. Ssobolew[10] reported fifteen cases in which the islands were either absent altogether, or were much diminished in number. Weichselbaum and Stangl,[12] Herzog,[11] and Opie[23] have described instances in which interacinar islands were diminished. Two factors probably contribute to explain this diminution. First, there is a group of cases in which the pancreas may show little or no change, and where the condition is perhaps due to a congenital defect. As Opie has pointed out, pancreatic development is subject to wide variations, irregularities in the size and relation of the ducts being of frequent occurrence. He reports the case of a child, fourteen years old, with hereditary diabetes, in which the number of islands showed a well-marked diminution.

In a second group of cases, the scarcity of islands of Langerhans is associated with chronic interacinar pancreatitis of severe type. Here the islands of Langerhans are probably destroyed, and their places occupied by fibrous tissue. In these cases, small patches of sclerosis, often seen within the lobules, suggest obliterated islands, while in other places islands of Langerhans are found only partially replaced by the fibrous material.

In nineteen of my cases the islands of Langerhans showed a marked diminution in number, recognizable by inspection of sections. These nineteen cases may be classified as follows:

1. Scarcity of islands in a normal pancreas, 5.
2. Scarcity of islands in association with a mild chronic interacinar pancreatitis, 9.
3. Scarcity of islands associated with advanced chronic interacinar pancreatitis, 6.

The average size of the islands differed considerably in this group of cases.

In thirty-four of my cases, sections from both the head and tail were examined. No notable differences in the character of the islands of Langerhans were found in the two portions. The interacinar islands, however, were generally more numerous in the tail.

Cases in which the Pancreas was Normal.

Eleven of my cases showed no discoverable anatomical lesion in the pancreas. The pancreas in two cases of this group (Cases VII and LVII) was described as small, but in all other respects the gross appearance agreed with the microscopic in suggesting no pathological changes. In five cases, diminution in the number of interacinar islands was marked. The islands were of small size in five cases. The age in all but one of these cases with normal pancreas was under thirty-five years.

Relationship of Diabetes to Organs Other than the Pancreas.

I have already discussed the relation of pancreatic lesions occurring with diabetes to general or pancreatic arteriosclerosis.

Cirrhosis of the liver was present in seven of my cases. The pancreas from all of these cases showed well marked interacinar inflammation, which in two instances was far advanced. One etiological factor is probably active in both organs. The same statement is perhaps applicable to chronic nephritis, which was present in twenty-five cases, and was in all instances associated with more or less advanced chronic inflammation of the pancreas. It has long been realized that the sclerosis which comes on in the latter part of life, attacking first the arterial walls and later one or more of the viscera, is a general process, which may be selective, involving in its action chiefly one or more organs.

Two cases of cirrhosis of the liver were accompanied by *hæmochromatosis* (Cases XLII and LIX). This remarkable disturbance of iron-metabolism was first described by von Recklinghausen,[28] and is characterized by deposition of a brown iron-containing pigment in the various tissues and organs of the body. Hæmochromatosis with diabetes, or "bronzed diabetes," is well recognized. Von Recklinghausen found cirrhosis of the liver a constant feature of the disease, and more recently a number of writers have noted the occurrence of chronic interstitial pancreatitis.

Case XLII was obtained through the kindness of Dr. MacCallum of the Johns Hopkins Hospital, and will be reported in detail. A man, thirty-seven years of age, gave a history of diabetes of nine months' standing. The urine contained 6.5% of glucose. Acetone and diacetic acid were also present. There were ascites and pigmentation of the skin. The patient died in coma. At autopsy, marked pigmentation was found in the liver, heart, pancreas, lymph glands and skin. The liver showed cirrhosis and the heart was hypertrophied. The pancreas was large and firm and weighed 150 grammes. On section it was brown, and mottled with fat. Microscopically, there is a very marked infiltration of fat tissue which appears to have replaced the glandular structures in many places. This invasion is not confined to the interlobular tissue but separates the acini as well. There is also a definite new growth of connective tissue between the acini, which is rich in spindle cells and infiltrated with a moderate number of lymphoid and plasma cells. The interstitial tissue is the seat of an abundant deposition of light-brown pigment which reacts positively to the chemical test for iron. Many of the acinar cells are loaded with this pigment. Some of the acini are considerably swollen, and their cells stain faintly. The walls of the blood-vessels are not appreciably thickened.

The islands of Langerhans are very scarce, and considerably smaller than the normal, none of them measuring over 200 microns in diameter. The fibrous capsules about the islands are thickened and infiltrated by pigment. Many of the island cells also contain pigment and their nuclei stain poorly.

Case LIX was obtained through the kindness of Dr. Wright, of the Massachusetts General Hospital. A man, forty-five years of age, had had three per cent. of glucose in his urine, as well as acetone and diacetic acid. The patient died in coma, and at autopsy there were found cirrhosis of the liver and pigmentation of the liver and pancreas. The pancreas was dark brown in color and rather soft.

Microscopically, sections from the pancreas show a marked new growth of connective tissue between the acini. The lobules are widely separated by adipose tissue. The stroma is the seat of a universal deposition of iron pigment which stains blue with ferrocyanide of potassium and hydrochloric acid. Many of the acinar cells are also loaded with pigment. The walls of the blood-vessels are somewhat thickened. Dense collections of lymphoid and polymorphonuclear cells are found in the neighborhood of the larger ducts. The islands of Langerhans are fairly numerous and normal in size; many of them are surrounded by capsules of fibrous tissue, and the insular capillaries are slightly thickened. A considerable number of insular cells are distended with pigment, and give evidence of degeneration, the nuclei staining indistinctly.

The islands in these two cases show similar lesions, namely, encapsulation by fibrous tissue and a deposition of iron pigment in the insular cells. In the case first described there was a marked diminution in the number of the islands of Langerhans, probably partly due to the advanced lipomatosis.

The association of diabetes with certain diseases of the ductless glands has been frequently observed. Hansemann[17] collected from the literature of the subject, fifteen cases of *exophthalmic goitre* which had been accompanied by diabetes, but there had been no opportunity to study the pancreas. A number of writers have more recently observed glycosuria in connection with Grave's disease. Falta, Eppinger and Rudinger[32] have studied the relationship between the pancreas and the ductless glands—more particularly the thyroid and suprarenal glands. By removing one or more of these organs and observing the effect on metabolism, they claim to have established a definite relation between the three organs. They believe that the adrenal glands, with the aid of the thyroid, are engaged in "mobilizing" the sugars, while the pancreas is concerned in their oxidation. A lesion in any one of the three organs may, perhaps, disturb the equilibrium between the supply and the consumption of carbohydrates and produce glycosuria. These speculations serve to emphasize the well-known relationship between diabetes and diseases associated with lesions of the thyroid and adrenals.

I have been able to include in the present series one case of diabetes which was associated with exophthalmic goitre; the case was reported by Dr. Morris Manges in the Mt. Sinai Hospital Reports, Vol. II. Dr. Libman was kind enough to supply me with a part of the pancreas.

The patient, a woman, forty-four years of age, gave a history of diabetes of six months' duration, her chief complaint being weakness, emaciation and thirst. The urine contained five per cent. of glucose. Acidosis was present. There were marked exophthalmos, tachycardia and neuralgic pains. Death occurred from asthenia and cardiac failure. At autopsy the thyroid gland was enlarged and firm; microscopically there were glandular hyperplasia and chronic inflammation. The pancreas was atrophic and weighed forty-five grammes; on section it was pale and soft.

Microscopically the pancreas exhibits typical chronic interacinar pancreatitis of advanced grade. The acini are small and separated by dense fibrous tissue, which in some places has almost completely replaced the parenchyma. The stroma shows rich infiltration by lymphoid and plasma cells, with a few polymorphonuclear leucocytes. The vessel walls are thickened and hyaline. Islands of Langerhans are of rather small area. In places where the sclerosis is severe the interacinar islands are much involved, being buried in dense fibrous tissue and invaded by the same material. Many of them have been almost obliterated by the fibrous hyperplasia.

Adenoma of the thyroid gland has been noted in the anatomical diagnosis in two of my cases with diabetes (Cases XXIX and XXXIV).

It is significant in this connection that in both cases the adenoma-like hypertrophy of the islands of Langerhans, described above, is present. In Case XXXIX, this hypertrophy affects nearly all the islands of Langerhans, many of which attain great size. In Case XXXIV, the insular hypertrophy is also well marked. The pancreas in both of these cases also shows a well marked chronic interacinar inflammation, with considerable increase of fibrous tissue in and about the islands of Langerhans.

Myxœdema was found associated with diabetes in one of my cases (Case VI). The patient, a woman seventy-four years of age, was first admitted to the Presbyterian Hospital on March 12th, 1899, complaining of weakness, shortness of breath, despondency and gradual loss of mental powers.

There was general thickening of the subcutaneous tissue; the skin was dry and scaly and the nails and hair were brittle. There was puffiness under the eyes and the tongue was thickened. Speech was deliberate and lisping in character. Pulse tension was high. At this time there was no glucose in the urine. The patient was treated with thyroid extract and improved rapidly.

A year and a half later, the patient was admitted again to the hospital, complaining of thirst, polyuria, pruritus vulvæ and eczema. Myxœdema was much improved. The urine contained four per cent. of glucose. The amount of sugar diminished under treatment. During the two years following the patient was in the hospital several times, and finally died in coma Sept. 6th, 1902.

At autopsy the thyroid weighed only eight and a half grammes; microscopically there is very advanced atrophy of the parenchyma. The alveoli have been almost completely obliterated and their places are occupied by fibrous tissue, densely infiltrated in places by lymphoid cells.

The pancreas weighed one hundred and twenty grammes, and was of tough consistency. Microscopically advanced chronic interacinar inflammation and universal infiltration of adipose tissue can be recognized in spite of extensive post-mortem digestion. The islands can be identified and show considerable sclerosis.

The occurrence of glycosuria with *acromegaly* has been observed in a considerable proportion of cases of this disease. Hansemann, Dallemange, and others have described such cases in which chronic interstitial pancreatitis was found. Through the kindness of Dr. Norris, I have been able to study the pancreas from a case of acromegaly, which was accompanied by diabetes.

The case was reported by Dr. Norris in the Proceedings of the New York Pathological Society, February, 1907.

The patient, a man thirty-three years old, was admitted to Bellevue Hospital with the following symptoms: Progressive enlargement of jaw, nose, ears, hands and feet. Persistent frontal headaches, and attacks of vertigo. Gradually increasing loss of vision, ending in atrophy of both optic nerves and almost complete blindness. There were recurrent epileptiform attacks. Glycosuria had been present during twenty-two months.

At autopsy, a large tumor was found, connected by a broad pedicle to the pituitary gland, which was itself enlarged; microscopically, the tumor is composed of cuboidal or oval cells which are arranged in irregular alveoli. The stroma is very scanty. The alveoli are separated by capillaries, whose endothelial lining is apparently in direct contact with the alveolar cells. In some places the capillaries are dilated, giving the tumor a very vascular appearance.

The pancreas was large and firm, and weighed one hundred and seventy grammes. The lobulation was distinct and no macroscopic lesions were noted.

Microscopically, the pancreas is free from interstitial induration. There has been some post-mortem digestion in a few places but otherwise the glandular acini are normal in appearance. The walls of the blood vessels are slightly thickened. The islands of Langerhans are numerous, irregular in outline, and larger than the normal. One island is found which measures six hundred micromillimeters in diameter. Many of the larger islands present a very unusual appearance. The insular cells are large, and often columnar in shape and arrangement. In many instances, the cords of cells form partial or complete circles, whose lumina contain the insular capillaries. These capillaries often show definite sclerosis. There is a marked deposit of hyaline material in a few of the islands of Langerhans.

The coexistence of this adenoma-like hypertrophy of the islands of Langerhans, with adenoma of the pituitary gland, is especially significant if it be borne in mind that the same type of insular hypertrophy was observed in association with the two cases of adenoma of the thyroid gland. At present I can offer no satisfactory explanation of this association.

In another case (Case LXXXIII) *calcification of the pituitary gland* is mentioned as one of the anatomical findings. A well-marked chronic interstitial inflammation, which affects chiefly the interacinar tissue, is found in the pancreas. The islands of Langerhans are small and rather scanty. They show definite fibrous changes, manifested by a thickening of the capillary walls.

In two of my cases *atrophy of the adrenal glands* was noted in the anatomical diagnosis (Cases XXVI and LXXXI). Both of these cases showed advanced arteriosclerosis and gangrene of the extremities. The pancreas, in both instances, is the seat of advanced sclerosis of the interacinar type. In many places the acini are scanty and atrophic in appearance, being everywhere surrounded and compressed by the newly formed tissue. The vessel walls are thickened. The islands of Langerhans are buried in dense patches of fibrous tissue, and are themselves markedly invaded by the same material.

Other anatomical changes associated with diabetes are of considerable interest. *Gangrene* is a common complication, and is generally attributed to two causes, arteriosclerosis and lowered resistance in the tissue, resulting from the diabetes. Gangrene occurred in fifteen of my cases and was in all instances associated with arteriosclerosis and well-marked chronic interacinar pancreatitis. The youngest individual affected by gangrene was forty-three years of age. In eleven cases it was the lower, and in two, the upper extremity which was involved. There was one case of gangrene of the scrotum and one case in which the location of the gangrene was not mentioned.

Fat necrosis has been found to occur with various lesions of the pancreas, and accompanies the acute, more often than the chronic changes. Fat necrosis is mentioned in the anatomical diagnosis of four cases in the present series. I have been unable to find any common feature other than chronic interacinar induration present in these cases.

Cholelithiasis occurred in nine of my cases. Opie[29] has shown that where gall-stones are a causal factor in chronic pancreatitis, they produce sclerosis of the interlobular variety. The inflammatory process in these seven cases was definitely interacinar; it is probable, therefore, that the gall-stones were not related etiologically to the pancreatic lesions.

Pathogenesis of Diabetes Mellitus.

The islands of Langerhans are composed of columns of cells, with a rich vascular supply, but have no communication with the ducts. In this respect they resemble the parenchyma of the thyroid and adrenal glands. If the pancreas furnishes an internal secretion, it is possible that this function is performed by the islands of Langerhans. Attempts to study these islands experimentally are met by great difficulties. Marked sclerosis of the pancreas follows ligation of the pancreatic duct in animals but the islands of Langerhans remain normal and no glycosuria occurs. A similar lesion unaccompanied by diabetes occurs as the result of occlusion of the pancreatic duct in man.

A number of observers believe that the islands of Langerhans are phases in the life-history of the secreting alveoli, and are not independent structures. Dale[30] claims to have converted acini into islands of Langerhans by starvation and the injection of secretin. The observations of Dale have not been confirmed. It is possible that Dale mistook for islands groups of acini exhausted by hypersecretion and similar to areas which, as previously mentioned, occur in diabetes and fail to exhibit the staining reaction of secreting acini. The peculiar structure and blood supply of the islands of Langerhans and the characteristic staining reactions which Lane[31] has demonstrated, furnish strong evidence in favor of their independence.

In the present study of the pancreas from ninety cases of diabetes, the following pancreatic changes have been encountered:

1. Chronic Inflammation of the Pancreas:	
Interacinar pancreatitis; sclerosis of islands of Langerhans	39
Interlobular pancreatitis; sclerosis of islands of Langerhans	4
Interacinar pancreatitis; hyaline degeneration of islands of Langerhans	19
Interacinar pancreatitis with lipomatosis; sclerosis of islands of Langerhans	2
Interacinar pancreatitis with lipomatosis; hyaline degeneration of islands of Langerhans	1
Interacinar pancreatitis; with siderosis of islands of Langerhans (Hæmochromatosis)	2
2. Parenchyma normal; lesions of the islands of Langerhans:	
Sclerosis of the islands of Langerhans	4
Hyaline degeneration of the islands of Langerhans	7
Infiltration of leucocytes about islands of Langerhans	1
3. Pancreas normal	11
	90

Of the eleven cases of normal pancreas, five showed a marked diminution in the number of islands of Langerhans. In one other case the pancreas was abnormally small.

In order to establish causal relationship between lesions of the islands of Langerhans and pancreatic diabetes, the following premises must be proven:

(I). Lesions of such a nature as to interfere with the performance of their function occur in the islands in diabetes.

(II). These lesions are primary and not secondary to diabetes.

(1). The chief object of this study has been to determine the frequency of lesions of the islands of Langerhans in diabetes. Eighty-eight per cent. of my cases have shown definite changes in these bodies. In thirty per cent. of cases, some or all of the islands of Langerhans exhibited hyaline degeneration with consequent partial destruction. Lesions of the islands of Langerhans have usually been associated with chronic interacinar pancreatitis and arteriosclerosis. In twelve cases insular changes have occurred in an otherwise normal pancreas.

Are the lesions of the islands of Langerhans sufficiently severe to produce loss of function?

In most instances, there can be little doubt that hyaline degeneration and sclerosis have an injurious effect. Even where there is only a moderate thickening of the insular capillaries, the change is doubtless sufficient to interfere with the proper nutrition of the cells.

(2). Are lesions of the islands of Langerhans secondary to diabetes?

There is no evidence in support of this view. The variety of lesions of these structures, associated with diabetes, affords evidence that they are not the result of the same cause. As a rule sclerosis of islands of Langerhans is associated with a chronic interacinar pancreatitis; diabetes with a destructive lesion of the pancreas, is comparable to diabetes following removal of the gland in lower animals.

In cases where the parenchyma is normal, sclerosis of the islands of Langerhans is limited to the capillary wall and appears to be part of a general arteriosclerosis.

Is the cause of pancreatic diabetes to be found in lesions of the parenchyma, in lesions of the islands of Langerhans, or in both combined?

Chronic interacinar pancreatitis alone does not answer the question, for both structures are implicated. On the other hand, with forms of chronic inflammation due, for example, to duct obstruction, where the parenchyma is destroyed and the islands of Langerhans remain intact, the absence of diabetes indicates that destruction of the glandular acini is not sufficient to produce the disease.

Most significant, however, are cases with partial or complete destruction of the islands of Langerhans and no changes in the parenchyma. Twelve cases in the present series have shown lesions of this character. In seven of these the interacinar islands were hyaline, in four they were sclerotic, and in one they were infiltrated by polymorphonuclear and lymphoid cells. The selective character of these lesions is strong evidence in favor of the view that the islands stand in a causal relationship to diabetes.

The frequency of hypertrophy of the islands of Langerhans in diabetes is noteworthy. In forty per cent. of my cases islands of Langerhans measuring four hundred micromillimeters or more in diameter have been found. Hypertrophy of the islands has usually been associated with sclerosis or hyaline degeneration affecting other interacinar islands in the same gland, and is probably compensatory in character.

How may the occurrence of a normal pancreas with diabetes be explained?

It is possible that diabetes in some of these cases is not of pancreatic origin. It is well known that temporary glycosuria can be caused by puncture of the fourth ventricle and by other injuries of the nervous system. Falta, Eppinger and Rudinger,[32] in their studies of the relationship of the pancreas to the ductless glands, reach the conclusion that the latter are almost equally instrumental with the pancreas in the production of diabetes. It is significant, however, that in the cases of this series in which diabetes has accompanied lesions of the ductless glands, for example, exophthalmic goitre and myxœdema, well-marked changes in the pancreas and in the islands of Langerhans have been found.

It has been said by Sauerbeck that the occurrence of normal pancreas in association with diabetes mellitus does not furnish evidence that lesions of the islands of Langerhans do not cause glycosuria, for it is equally unfavorable to the view which refers glycosuria to changes in the secreting parenchyma.

Diminution in the number and size of the islands of Langerhans in an otherwise normal pancreas may play an important part in the production of diabetes, particularly in young individuals, and a deficiency of this kind is perhaps congenital. An abnormally small pancreas is associated with diminution of the number of islands of Langerhans, even though their numerical relation to the secreting parenchyma is normal.

Conclusions.

1. Anatomical lesions of the pancreas occur in more than seven-eighths of all cases of diabetes mellitus.

2. In diabetes associated with lesions of the pancreas, the islands of Langerhans constantly show pathological changes (sclerosis, hyaline degeneration, infiltration of leucocytes, and hypertrophy).

3. In some cases of pancreatic diabetes (twelve of ninety cases) the lesion of the pancreas is limited to the islands of Langerhans.

4. In fifteen cases of diabetes mellitus, associated with hyaline degeneration of the islands of Langerhans, the average duration of the disease has been three and a half years; in six cases of diabetes mellitus, associated with an infiltration of round cells and leucocytes about the islands of Langerhans, the average duration of the disease has been eleven months.

5. Destructive lesions of the islands of Langerhans may be associated with compensatory hypertrophy of other interacinar islands.

6. Peculiar adenoma-like hypertrophy of the islands of Langerhans occurs in a small proportion of cases (seven of ninety), and may be associated with adenomata of the thyroid gland (two cases), and of the pituitary body (one case).

7. Diabetes mellitus occurring in association with hæmochromatosis (bronzed diabetes), is referable to pigmentation and destruction of the islands of Langerhans.

8. The pancreas is found to exhibit no pathological changes in twelve per cent. of cases. In approximately one-half of these cases it has been noted that the size of the gland or the number of islands is much less than normal.

9. Fifty per cent. of cases of diabetes mellitus occurring before the age of thirty years are associated with lesions of the pancreas (seventy-five per cent. of all cases of diabetes mellitus in which the pancreas is normal occur before the age of thirty years); ninety-seven per cent. of cases of diabetes occurring after the age of thirty years are associated with lesions of the pancreas, and eighty-nine per cent. occur in association with chronic interacinar pancreatitis accompanying arteriosclerosis.

10. Interacinar pancreatitis, which occurs in seventy-three per cent. of all cases of diabetes, is almost constantly associated with arteriosclerosis; gangrene of the extremities, which occurs in one-fifth of all cases of interacinar pancreatitis, is doubtless referable to the same cause.

11. Chronic interlobular pancreatitis, when associated with diabetes, is accompanied by sclerosis or hyaline degeneration of the islands of Langerhans.

12. Diabetes, in association with myxœdema or with exophthalmic goitre, may be referable to a lesion of the pancreas, namely, chronic interacinar inflammation with sclerosis of the islands of Langerhans; diabetes, in association with acromegaly, may be

referable to a lesion of the islands of Langerhans, namely, sclerosis and hyaline degeneration with adenoma-like hypertrophy.

In closing I wish to express my gratitude to Dr. Opie for much assistance and many valuable suggestions. I am indebted to Dr. Thacher for twenty-one cases collected in this laboratory; to Dr. Wright for eighteen cases from the Massachusetts General Hospital; to Dr. Mallory for five cases from the Boston City Hospital; to Dr. Libman for eight cases from Mt. Sinai Hospital; to Dr. Longcope for three cases from the Pennsylvania Hospital; to Dr. Oertel for six cases from the New York City Hospital; to Dr. Norris for two cases from Bellevue Hospital; to Dr. Adami and to Dr. Klatz for twelve cases from the Royal Victoria Hospital of Montreal; to Dr. Duval and Dr. White for five cases from the Montreal General Hospital; to Dr. MacCallum for five cases from the Johns Hopkins Hospital; to Dr. Wood for one case from St. Luke's Hospital; and to Dr. James and Dr. Stein for material from private cases.

SYNOPSIS OF CASES.

CASE I. Presbyterian Hosp. S. S., m., 72 yrs. Turk. No history. Died with pneumonia. Glucose 3.6%. Anat. Diag.:—Diabetes, pneumonia, fatty liver. *Pancreas:*—Wt. 112 gms.; small hard. Mic.:—Moderate chronic interacinar pancreatitis. Arterial walls thickened and hyaline. Considerable fibrosis of islands, which are larger than normal, largest 700 microns in diam.

CASE II. Presbyterian Hosp. Mann., m., 10 yrs. U. S. Onset of diabetes acute; duration 8 mos.; glucose 5%; acidosis. Considerable loss of weight. Died with pneumonia. Anat. Diag.:—Diabetes, broncho-pneumonia, fibrinous pleuritis, pelvic cellulitis. *Pancreas:*—Wt. 30 gms. No gross lesions. Mic.:—Struma quite cellular; islands numerous; insular cells small and closely packed together. Pancreas otherwise normal.

CASE III. Presbyterian Hosp. Schn., m., 69 yrs. French. No history obtained; glucose 4.5%; marked acidosis. Died with pneumonia. Anat. Diag.:—Diabetes; pneumonia; arteriosclerosis; chronic nephritis. *Pancreas:*—Wt. 120 gms. Imbedded in fat; tough and nodular; on section, fatty and cirrhotic. Mic.:—Well marked chronic interacinar pancreatitis. Moderate amount of fat. Vessel-walls thickened. Atrophy of acini. Islands scant but some are large. Considerable fibrosis of islands. A few of them hyaline. Largest island 650 microns in diam.

CASE IV. Presbyterian Hosp. Dres., f., 71 yrs. German. Gradual onset of diabetes; duration 22 yrs.; glucose 5%; acidosis. Died with pneumonia. Anat. Diag.:—Diabetes; pneumonia; cardiac disease; chronic nephritis. *Pancreas:*—Wt. 100 gms. Hard, otherwise normal. Mic.:—Moderate chronic interacinar pancreatitis. Arterial walls thickened; islands large; considerable fibrosis of islands.

Case V. Presbyterian Hosp. Mal., m., 24 yrs. U. S. Acute onset of diabetes; duration 2½ mos.; glucose 6.3%; acidosis. Rapid loss of weight; died in coma. Anat. Diag.:—Diabetes. *Pancreas:*—Wt. 60 gms. Soft, flabby, with very little fat; lobules distinct. Extravasation of blood. Mic.:—Parenchyma normal. Islands large. Well-marked fibrosis of islands. Infiltration of lymphoid cells about some of the islands.

Case VI. Presbyterian Hosp. P., f., 74 yrs. U. S. Admitted with weakness, shortness of breath, and loss of mental powers. General thickening of the subcutaneous tissues; skin dry and scaly; nails and hair brittle. Puffiness under eyes; tongue thickened. Speech deliberate and lisping. Pulse tension high. No glucose in urine. Thyroid extract produced great improvement. Patient readmitted to hospital 18 mos. later, complaining of thirst, polyuria, pruritis vulvæ, and eczema. Urine contained 4% of glucose. Duration of diabetes less than 18 mos. Patient died in coma. Anat. Diag.:—Diabetes; myxœdema; chronic endocarditis. *Pancreas:*—Wt. 120 gms. Tough but flabby, cut surface deep red. Mic.:—Marked chronic interacinar pancreatitis with considerable fat infiltration. Vessel-walls thickened and calcified. Autolysis. Only a few islands recognized; these are sclerotic.

Case VII. Presbyterian Hosp. Bon., m., 32 yrs. U. S. Duration of diabetes 3 yrs.; glucose in large amount. Died with pneumonia. Anat. Diag.:—Diabetes; pneumonia; pulmonary tuberculosis. *Pancreas:*—Wt. 30 gms. Very small; tissue flabby; otherwise normal. Mic.:—No interstitial sclerosis; pink-staining acini. Islands very scarce, but appear normal.

Case VIII. Presbyterian Hosp. Ber., m., 51 yrs. German. Duration of diabetes several years. Admitted after a sunstroke with very high temperature. Glucose 5%; no acetone. Gangrene of scrotum. Anat. Diag.:—Diabetes; pulmonary tuberculosis; fatty liver; hypertrophy of spleen; gangrene of scrotum. *Pancreas:*—Wt. 120 gms. A little fatty, about normal size. Mic.:—Considerable chronic interacinar pancreatitis; infiltration of stroma with lymphoid and plasma cells, and a few polymorphonuclear leucocytes. Vessel-walls thickened and hyaline. Considerable fat tissue between lobules. Acini atrophic in places. Well-marked sclerosis of islands. Island cells small. Number of islands rather small.

Case IX. Presbyterian Hosp. Fl., m., 58 yrs. German. No history. Glucose in large amount. Died in coma. Anat. Diag.:—Diabetes; pulmonary tuberculosis; gall-stones. *Pancreas:*—Normal in appearance. Mic.:—Marked chronic interacinar and slight interlobular sclerosis, considerable infiltration of lymphoid and plasma cells, with a few polymorphonuclear leucocytes. Adipose tissue rather abundant. Vessel-walls thickened and hyaline. Extensive atrophy of parenchyma. Islands very sclerotic; insular cells shrunken. Islands large and numerous (some 525 microns in diam.). Considerable autolysis in parts of these sections.

Case X. Presbyterian Hosp. Dem., m., 51 yrs. U. S. Duration of diabetes 2 yrs. Marked loss of weight and strength. Glucose 10%. Died in coma (?). Anat. Diag.:—Diabetes; pulmonary tuberculosis; gall-stones. *Pancreas:*—Wt. 60 gms. Very slender; on section, apparently normal. Mic.:—Well-marked chronic interacinar pancreatitis; stroma very cellular with considerable infiltration of lymphoid cells. Arterial walls thickened. Cells of parenchyma and of islands appear small. Capillaries of islands thickened.

Case XI. Presbyterian Hosp. Brus., f., 60 yrs. German. No history. Brought in comatose; glucose considerable quantity. Anat. Diag.:—Diabetes; fat necrosis; cerebral hemorrhage; cardiac hypertrophy; gall-stones. *Pancreas:*—Wt. 60 gms. Much invaded by fat. In places, numerous pink-white specks on cut surface. Mic.:—Well-marked chronic interacinar pancreatitis; considerable infiltration of lymphoid and plasma cells. Arteries thickened and hyaline. Islands of usual size and show considerable sclerosis.

Case XII. Presbyterian Hosp. Sn., f., 57 yrs. Eng. Onset of diabetes gradual; duration 1 yr. Glucose 3.3%. Died in coma (?). Anat. Diag.:—Diabetes; chronic endocarditis; slight cerebral softening. *Pancreas:*—Wt. 90 gms. On section the surrounding adipose tissue dips in considerably. Mic.:—Well-marked chronic interacinar pancreatitis; considerable infiltration of lymphoid and polymorphonuclear cells. Arteries thickened and hyaline. Islands larger than normal (some are 500 microns in diam.) and show sclerosis and hyaline degeneration.

Case XIII. Presbyterian Hosp. Sill., m., 27 yrs. U. S. 3 yrs. ago noticed weakness and gradual loss of weight. Enormous thirst and appetite. Loss of weight 35 lbs. Severe pain in legs. Glucose, 11%, was reduced under treatment; acetone and diacetic acid present. Before death patient had high fever and was irrational. Leucocytes 24,000. Anat. Diag.:—Diabetes; gastroptosis. *Pancreas:*—Wt. 60 gms. On section, normal. Color slightly yellowish. Mic.:—Sections from head and tail show no lesions. Islands remarkably diminished in number, and of small size, the largest measuring only 200 microns in diameter.

Case XIV. Presbyterian Hosp. B., f., 30 yrs. Irish. No history. Brought in comatose. Glucose in large quantity. Anat. Diag.:—Diabetes; pneumonia. *Pancreas:*—Wt. 45 gms. Normal in appearance. Mic.:—Well-marked, but focal, interacinar pancreatitis. Arteries thickened and hyaline. Islands small in number and show considerable sclerosis; quite a number are hyaline.

Case XV. Presbyterian Hosp. Lind., m., 35 yrs. Swede. Onset marked by weakness, thirst, and polyuria. Improved under treatment. Readmitted day before death, with intense abdominal pain. Died in coma. Glucose 4.4%. Acetone, diacetic and *B*-oxybutyric acid present. Duration of disease, 9 mos. Anat. Diag.:—Diabetes; acute gastritis; arteriosclerosis. *Pancreas:*—Wt. 120 gms. Firm, of good size, pale pink in color. Cut surface pale; lobulation indistinct; islands not visible. Mic.:—Moderate grade of chronic interacinar pancreatitis. Well-marked infiltration of lymphoid and plasma cells, eosinophiles, and polymorphonuclear leucocytes. Arteries thickened. The number of islands both in head and tail is quite small. Moderate thickening of insular capillaries.

Case XVI. Presbyterian Hosp. Wh., f., 60 yrs. U. S. No history. Anat. Diag.:—Diabetes; chronic nephritis; chronic pulmonary tuberculosis. *Pancreas:*—Wt. 100 gms. Surface appears to be invaded by fat; section looks normal. Mic.:—Well-marked chronic interacinar pancreatitis. Arteries thickened. Considerable sclerosis of islands. A few of the islands are very large (650 microns in diam.); in some islands the cells are columnar in shape and exhibit an adenoma-like arrangement.

CASE XVII. Presbyterian Hosp. La T., m., 52 yrs. U. S. Admitted to hospital for gangrene of foot. Glucose 4.25%. Duration of diabetes 15 mos. Anat. Diag.:—Diabetes; pneumonia; gangrene of foot; fatty heart. *Pancreas:*—Wt. 185 gms. Rather large; somewhat hard and tough on section. Mic.:—Considerable chronic interacinar pancreatitis, most marked in head; abundant infiltration of lymphoid and plasma cells. Arteries thickened and hyaline. Islands quite scanty and show considerable sclerosis.

CASE XVIII. Presbyterian Hosp. Odg., f., 75 yrs. Eng. No history. Anat. Diag:—Diabetes; thrombosis of heart; pulmonary infarction; ununited fracture of femur; hypertrophy of heart; nutmeg liver; chronic nephritis. *Pancreas:*—Some fat infiltration. Mic.:—Well-marked chronic interacinar pancreatitis, stroma cellular and infiltrated at points by numbers of lymphoid cells. Considerable fatty infiltration. Arteries thickened. Islands numerous, and show considerable sclerosis; a number of them are hyaline.

CASE XIX. Presbyterian Hosp. W., m., 27 yrs. U. S. No history. Anat. Diag.:—Diabetes; necrosis of lungs; broncho-pneumonia; slight nephritis. *Pancreas:*—Wt. 90 gms. Appears normal, though pale. Mic.:—Parenchyma is the seat of a mild sclerosis. Some acini are larger than normal. Considerable infiltration of fat. Arteries slightly thickened. Islands very small in number and area; island capillaries definitely thickened.

CASE XX. Presbyterian Hosp. Van W., m., 64 yrs. U. S. No history found. Anat. Diag.:—Diabetes; chronic pulmonary tuberculosis; chronic nephritis; gangrene of foot; fatty liver. *Pancreas:*—Wt. 60 gms. Rather small; a good deal of fat surrounding and invading gland. Mic.:—Considerable increase of interacinar connective tissue. Arteries thickened and hyaline. Atrophic acini in places. Islands very scarce, and show considerable sclerosis.

CASE XXI. Case of Dr. James. F., 36 yrs. Duration of diabetes 1 yr. Persistent vomiting. Acidosis. Died in coma. Glucose 2.8%. Anat. Diag.:—Diabetes; fat necrosis; fatty liver. *Pancreas:*—Very firm. Mic.:—Marked increase of both the interlobular and the interacinar connective tissue. Dense infiltration of lymphoid, plasma, and polymorphonuclear cells. Arteries thickened. Lumina of many acini are enlarged, and acini cells appear flattened and atrophic. Islands are larger than normal (some 600 microns in diam.). They show considerable sclerosis.

CASE XXII. Presbyterian Hosp. Mar., 1890. Only data obtainable in this case are from microscopical sections. They show a far advanced interlobular pancreatitis with considerable increase of the interacinar connective tissue. Well-marked atrophy of the parenchyma. Abundant infiltration of lymphoid cells. Acinar cells atrophic and flattened, the acinar lumen being larger than normal. Islands very scarce, and small in size; they all show considerable sclerosis. Several miliary tubercles found in the stroma.

CASE XXIII. Royal Victoria Hosp. 55, '97, m., 20 yrs. Eng. Three weeks in hospital. Disease ran acute course. Glucose 5%. Acetone and diacetic acid present. Rapid loss of weight. Died in coma. Anat. Diag.:—Diabetes;

multiple abscesses; nephritis; simple atrophy of pancreas. *Pancreas:*—Macroscopically was atrophied. Mic.:—No increase of interstitial tissue. Vessels normal. Acini in some places appear large. Some of the islands are surrounded by zones of polymorphonuclear and lymphoid cells and similar infiltration is often found about the insular capillaries. A number of giant islands are found, some measuring 600 microns in diam. A few islands show an adenoma-like hypertrophy.

Case XXIV. Royal Victoria Hosp. 73, '97, m., 31 yrs. Eng. 5 wks. in hospital. Diabetes ran an acute course. Glucose 6%; acetone and diacetic acid present. Died in coma. Anat. Diag.:—Diabetes; atrophy of pancreas, liver and spleen; fat necrosis; catarrhal colitis. *Pancreas:*—Wt. 40 gms. Marked atrophy. Mic.:—Moderate interacinar pancreatitis. Dense and wide-spread infiltration of polymorphonuclear leucocytes, which are concentrated in some places about areas of necrosis. Vessels thickened and hyaline. Islands quite large, irregular in outline. Island capillaries sclerotic. Many insular cells are columnar in shape and show a remarkable adenoma-like arrangement.

Case XXV. Royal Victoria Hosp. 32, '00, m., 65 yrs. Can. In hospital 4 yrs. with diabetes; glucose 3%. Anat. Diag.:—Diabetes; gangrene of foot; pulmonary tuberculosis; arteriosclerosis. *Pancreas:*—Wt. 150 gms. Rather small. Mic.:—Considerable increase of interacinar connective tissue. Infiltration of lymphoid cells at many points. Vessels much thickened and hyaline. Many acini atrophic. Islands numerous and of large size (some 500 microns in diam.). Islands sclerotic and in some instances hyaline.

Case XXVI. Royal Victoria Hosp. 95, '02, m., 75 yrs. Eng. Duration of diabetes 15 yrs.; died with pneumonia. Anat. Diag.:—Diabetes; gangrene; arteriosclerosis; cirrhosis of liver; atrophic adrenals; chronic nephritis. *Pancreas:*—Wt. 175 gms. Marked fatty infiltration. Mic.:—Very uneven new growth of the interstitial tissue, chiefly interacinar, and marked in places. Considerable infiltration of lymphoid cells. Vessels thickened and hyaline. Acini atrophic in some parts. Islands are large, bunched together, and very sclerotic. One island measures 1600 microns in diameter. Adenoma-like hypertrophy.

Case XXVII. Royal Victoria Hosp. 44, '03, m., 52 yrs. French Can. Duration of diabetes 15 yrs.; acute symptoms during 5 wks.; glucose 4%; acetone and diacetic acid present. Anat. Diag.:—Diabetes; boils; tuberculosis; acute diphtheritic colitis; chronic nephritis; acute splenitis; fatty heart. *Pancreas:*—Shrunken. Mic.:—A well-marked increase of the interacinar stroma, irregular in its distribution. Arteries thickened and hyaline. Islands bunched together in groups, and show considerable fibrosis.

Case XXVIII. Royal Victoria Hosp. 96, '03, m., 29 yrs. Eng. Duration 18 mos. Glucose 5%; acetone and diacetic acid present. Enormous gain in weight (155 lbs. in 18 mos.). Anat. Diag.:—Diabetes; obesity; chronic nephritis; pulmonary embolism; thrombosis of prostatic veins; portal cirrhosis of liver. *Pancreas:*—Wt. 150 gms. Marked fibrosis. Mic.:—There is a coarse, irregularly distributed sclerosis, chiefly interacinar, though the interlobular tissue is also increased in the neighborhood of the ducts and vessels. Considerable infiltration of fat. Arteries thickened and hyaline. Islands large and show considerable sclerosis.

Case XXIX. Royal Victoria Hosp. 79, '06, m., 70 yrs. French Can. Duration of diabetes 2 yrs. Glucose 2.9%; acetone and diacetic acid present.

Gradual loss of weight. Died in coma. Anat. Diag.:—Diabetes; fat necrosis; arteriosclerosis. Adenoma of thyroid and fatty thyroid. *Pancreas:*—Fatty infiltration of head. Mic.:—Well-marked interacinar pancreatitis. Vessels thickened. Some of the acini are larger than the normal. Islands very large (800 microns in diam. in some instances), and irregular in outline. Insular capillaries sclerotic. The cells of the islands are columnar in shape and show an adenoma-like arrangement.

CASE XXX. Royal Victoria Hosp. 130, '06, f., 21 yrs. Can. Diabetes ran acute course (1 yr. in duration). Glucose 8.5%; marked acidosis. Lost 40 lbs. in weight. Died in coma. Anat. Diag.:—Diabetes; pneumonia; fatty degeneration of liver; chronic nephritis; degeneration of adrenals. *Pancreas:*—Flabby, normal size. Mic.:—Entirely normal. Islands rather scarce, but of normal size.

CASE XXXI. Royal Victoria Hosp. 15, '07, m., 15 yrs. French Can. Diagnosis in this case was doubtful. Died with pulmonary œdema. Sugar was present in urine (1.5%) only on day of death. Anat. Diag.:—Diabetes; œdema of lungs; acute nephritis; persistent thymus; lymphatic hyperplasia. *Pancreas:*—Normal, macroscopically and microscopically. Islands normal in size, number and appearance.

CASE XXXII. Royal Victoria Hosp. 102, '07, f., 54 yrs. Can. No history. Anat. Diag.:—Diabetes; arteriosclerosis; thrombosis of coronary artery; cirrhosis of liver. *Pancreas:*—Atrophied, with much fat between the lobules. Mic.:—Well-marked, but focal interacinar sclerosis. Arteries thickened and hyaline. Islands numerous and definitely sclerosed; a few show hyaline degeneration.

CASE XXXIII. Royal Victoria Hosp. 144, '07, m., 56 yrs. Duration of diabetes 7 yrs. Glucose 7.7%; acetone and diacetic acid present. Loss of weight 50 lbs. Died of pneumonia. Anat. Diag.:—Diabetes; epithelioma of face, and base of skull; pneumonia. *Pancreas:*—Wt. 60 gms. Atrophied. Mic.:—Well-marked focal sclerosis, chiefly interacinar. Arteries thickened and hyaline. Islands are slightly sclerosed. Some of them show advanced hyaline degeneration.

CASE XXXIV. Royal Victoria Hosp. 14, '08, f., 38 yrs. Can. Duration of diabetes 3 mos. Glucose 4.1%; acetone and diacetic acid present. Loss of weight 30 lbs. Died in coma. Anat. Diag.:— Diabetes; adenoma of thyroid; red infarcts in liver and spleen; pneumonia; fatty liver; glycogenic infiltration of kidneys. *Pancreas:*—Hemorrhage into tail. Atrophy and fibrosis. Mic.:—Slight interacinar pancreatitis of a focal character, chiefly about the vessels and ducts. Arteries thickened and hyaline. Islands quite large and numerous. Some of them measure 600 microns in diameter. They are irregular in outline and show a definite adenoma-like arrangement of their cells, which closely resemble columnar epithelium. Dense infiltration of lymphoid cells about and within some of the islands. Insular capillaries sclerosed, and capsules thickened.

CASE XXXV. Montreal Gen'l Hosp. 89, '07, m., 28 yrs. Eng. Onset of diabetes acute; duration 7 wks. Glucose 3.5%; acetone considerable; diacetic acid present. Marked loss of weight. Died in coma. Anat. Diag.:—Diabetes; passive congestion of viscera. *Pancreas:*—45 gms. Small. Mic.:—No sclerosis between either the lobules or the acini. Considerable infiltration of polymorphonuclear and lymphoid cells in some places about the vessels, which are not sclerosed. Islands quite large; some of them 500 microns in diam. Moderate thickening of insular capillaries and capsules.

Case XXXVI. Montreal Gen'l Hosp. 64, '07, m., 58 yrs. French Can. This patient showed great gain in weight. Anat. Diag.:—Diabetes; obesity; hypertrophy of heart; chronic passive congestion of liver and spleen; chronic nephritis. *Pancreas:*—Fatty infiltration. Mic.:—Moderate interacinar pancreatitis. Some infiltration of polymorphonuclear and lymphoid cells. Marked fatty infiltration replacing parenchyma and widely separating lobules and acini. A few pink-staining acini. Arteries thickened. Number of islands quite small; they show definite sclerosis.

Case XXXVII. Montreal Gen'l Hosp. 48, '07, f., 66 yrs. French Can. Duration of diabetes 2½ yrs. Glucose 2%; acetone and diacetic acid present. Great loss of weight. Anat. Diag.:—Diabetes; gangrene of feet; pulmonary tuberculosis; fatty heart; marked arteriosclerosis; chronic nephritis. *Pancreas:*—Microscopically shows slight interacinar pancreatitis with rich infiltration of lymphoid, plasma and eosinophile cells. Arteries thickened and hyaline. Islands numerous and quite large (some of them 700 microns in diam.). They show considerable sclerosis and the majority of them show more or less advanced hyaline degeneration.

Case XXXVIII. Montreal Gen'l Hosp. 86, '08, m., 26 yrs. Scotch. Acute onset of diabetes; duration 8 wks. Glucose 2.5%; considerable acetone and diacetic acid present. Marked loss of weight. Died in coma. Anat. Diag.:—Diabetes; fatty liver; chronic nephritis. *Pancreas:*—Small. Mic.:—No sclerosis. Considerable infiltration of polymorphonuclear and lymphoid cells. Small arteries thickened. Islands large (some of them 500 microns in diam.). Islands show well-marked sclerosis, and there is infiltration of lymphoid and polymorphonuclear cells about some of them.

Case XXXIX. Montreal Gen'l Hosp. 9, '08, m., 26 yrs. Italian. Duration of diabetes 6 mos. Glucose 3.5%; acetone and diacetic acid present. Marked loss of weight. Died in coma. Anat. Diag.:—Diabetes; chronic nephritis; chronic pericarditis; cellulitis of leg; tuberculosis of abdominal glands. *Pancreas:*—Pale and soft. Mic.:—Moderate and unevenly distributed interacinar pancreatitis; considerable infiltration of lymphoid and plasma cells. Small arteries slightly thickened. Islands very small; largest measures only 150 microns in diam. Insular capillaries sclerotic. A few islands are hyaline.

Case XL. Johns Hopkins Hosp. 2152, m., 70 yrs. German. Duration of diabetes 7 yrs. Marked loss of weight. Glucose 2.7%; acetone and diacetic acid present on day of death. Died in coma. Anat. Diag.:—Diabetes; chronic nephritis; cardiac hypertrophy; arteriosclerosis; chronic pulmonary tuberculosis; chronic pleuritis; balano-posthitis. *Pancreas:*—Wt. 101 gms. Imbedded in fat, firm, with homogeneous red color; no fat invasion. Islands visible; ducts normal. Mic.:—Normal except for a slight thickening and hyaline degeneration of the vessels, and hyaline changes in some of the islands. The insular capillaries share in the arteriosclerosis.

Case XLI. Johns Hopkins Hosp. 2670. No history obtainable. Anat. Diag.:—Diabetes; stomach contents in bronchi; swelling of mesenteric lymph glands; acute vegetative endocarditis. *Pancreas:*—Wt. 38 gms. Normal size and consistency; grayish yellow; translucent. Duct normal. Mic.:—Parenchyma normal in every respect. No sclerosis. Islands small in number and size; largest measures only 200 microns in diam.

CASE XLII. Johns Hopkins Hosp. 2782, m., 37 yrs. Duration of diabetes 9 mos. Glucose 6.5%; acetone and diacetic acid present. Ascites and pigmentation of the skin. Disease ran acute course. Loss 26 lbs. Died in coma. Anat. Diag.:—Diabetes; hæmochromatosis; cirrhosis of liver; pigmentation of liver, heart, pancreas, lymph glands and skin; ascites; cardiac hypertrophy; chronic splenic tumor. *Pancreas:*—Wt. 150 gms. Large and firm. On section, brown and mottled with fat. Mic.:—Very marked infiltration of fat; parenchyma quite scanty. Moderate increase of interacinar connective tissue. Islands scarce and quite small; capsules thickened. The stroma, acinar cells and insular cells are in many places loaded with iron-containing pigment.

CASE XLIII. Johns Hopkins Hosp. 2929, f., 43 yrs. Negro. Admitted and died in coma. Glucose present in urine. Anat. Diag.:—Diabetes; gangrene of leg; pulmonary œdema; fatty liver; coronary sclerosis; chronic pelvic inflammation. *Pancreas:*—16x6 c.m. Normal shape; there are areas of atrophy; lobules larger in centre than at periphery; islands visible. Mic.:—Well-marked interacinar pancreatitis with rich infiltration of lymphoid cells. Arteries thickened and hyaline. The islands are scarce and smaller than the normal (largest measure only 200 microns). They show considerable sclerosis and some are hyaline.

CASE XLIV. Johns Hopkins Hosp. 2954, m., 57 yrs. Duration of diabetes 8 yrs. Glucose 3.2%; marked reactions for acetone and diacetic acid. Died in coma. Anat. Diag.:—Diabetes; pneumonia; gangrene of foot; chronic nephritis; fatty liver; arteriosclerosis; cystic thyroid. *Pancreas:*—Wt. 40 gms. 14 c.m. long. Very slender. Lobulation indistinct. Islands invisible. Ducts normal. Mic.:—Moderate interacinar pancreatitis; vessels thickened. Islands scarce and show moderate sclerosis.

CASE XLV. Mt. Sinai Hosp. H., m., 58 yrs. Glucose 5%; no acetone or diacetic acid. Duration of diabetes 10 yrs. Anat. Diag.:—Diabetes; coronary artery disease; chronic nephritis. *Pancreas:*—Very hard. Mic.:—Considerable interacinar sclerosis. Fatty infiltration. Arteries thickened and hyaline. Islands show considerable sclerosis.

CASE XLVI. Mount Sinai Hosp. Isr., f., 44 yrs. Russian. Glucose present in urine; no acetone or diacetic acid. Died in coma. Anat. Diag.:—Diabetes; pyelo-nephritis; cystitis. *Pancreas:*—Wt. 185 gms. Very much fat between lobules. Mic:.—Normal in appearance, except for a good deal of fat infiltration. Number of islands very small. A few pink-staining acini.

CASE XLVII. Mount Sinai Hosp. Kop., f., 32 yrs. Austrian. Died in coma day after admission. Glucose large amount; acetone and diacetic acid present. Anat. Diag.:—Diabetes; fibroids of uterus. *Pancreas:*—Firm. Mic.:—Well-marked increase of interacinar stroma. Marked infiltration of polymorphonuclear and lymphoid cells in some places. Vessels thickened and hyaline. The islands are moderately sclerosed.

CASE XLVIII. Mount Sinai Hosp. Hir., f., 44 yrs. Onset of diabetes acute; duration 6 mos. Marked loss of weight. Glucose 5%; acetone and diacetic acid present. Marked exophthalmos, tachycardia and neuralgic pains.

The latter were relieved by thyroid extract. Death occurred from asthenia and cardiac failure. Anat. Diag.:—Diabetes; hyaline struma with lime deposits (exophthalmic goitre); chronic pulmonary tuberculosis; chloasma cachectichorum (with iron-free pigmentation of skin and various organs); chronic nephritis; brown atrophy of heart; fatty liver. *Pancreas:*—Wt. 45 gms. 17 cm. long. Soft and atrophic. Mic.:—Considerable sclerosis of the interacinar type, irregularly distributed; abundant infiltration of lymphoid cells. Arteries thickened and hyaline. Acini atrophic in places. Many of the islands are markedly sclerotic and atrophic.

Case XLIX. Mount Sinai Hosp. Kauf., m., 56 yrs. German. Glucose 4.6%; no acidosis; died in coma. Anat. Diag.:—Diabetes; pulmonary tuberculosis; pyopneumothorax. *Pancreas:*—Long but small; otherwise normal. Mic.:—No sclerosis of parenchyma. Arteries thickened and hyaline. Islands show slight increase of fibrous tissue; most of them have suffered severe hyaline changes.

Case L. Mount Sinai Hosp. St., m., 75 yrs. Hebrew. Duration of diabetes 10 yrs. at least. Died suddenly from profuse hemorrhage from gastro-intestinal tract. Anat. Diag.:—Diabetes; arteriosclerosis; hemorrhage into gastro-intestinal tract (no break in mucosa found). *Pancreas:*—Wt. 100 gms. Soft. Mic.:—Moderate interacinar pancreatitis. Great and universally distributed fat infiltration; parenchyma reduced in amount. A few pink-staining acini. Islands numerous and large; they show moderate sclerosis, more noticeable in those islands isolated by the adipose tissue.

Case LI. Mount Sinai Hosp. Fat., m., 50 yrs. Hebrew. Duration of diabetes several years. Committed suicide. Anat. Diag.:—Diabetes; miliary tuberculosis. *Pancreas:*—Microscopically considerable interacinar sclerosis with abundant infiltration of lymphoid cells in some places. Arteries thickened and hyaline. Islands scarce and sclerotic.

Case LII. Mass. Gen'l Hosp. 823, f., 45 yrs. U. S. Duration of diabetes 6 mos. Glucose 2%. Anat. Diag.:—Diabetes; pelvic abscess; diphtheritic colitis; chronic nephritis; acute degeneration of liver and kidneys; otitis media; cystitis; lipoma of shoulder; excoriations of vulva; hyperostosis of skull. *Pancreas:*—Much diminished in breadth and thickness. At midpoint, cut surface measures 1 x 1.5 cm. Duct normal. Lobules grayish white, closely set. Tissue is harder than normal. Mic.:—Advanced interlobular and interacinar sclerosis, more advanced in head than tail. Dense infiltration of lymphoid cells in places. Parenchyma atrophic. Islands scarce and small; they show considerable sclerosis.

Case LIII. Mass. Gen'l Hosp. 831, f., 58 yrs. Irish. Duration of diabetes 2 yrs. Glucose, acetone and diacetic acid present. Anat. Diag.:—Diabetes; pulmonary tuberculosis; gall-stones; tapeworm; accessory spleen and liver. *Pancreas:*—Of good size and consistency. On section, normal. Mic.:—Moderate interacinar pancreatitis, vessels thickened and hyaline. Islands show considerable sclerosis and many are hyaline.

Case LIV. Mass. Gen'l Hosp. 833, m., 66 yrs. Duration of diabetes, which was mild, 9 yrs. Glucose 3.6%. Anat. Diag.:—Diabetes; carcinoma of stomach with metastases in cervical lymph glands; chronic pulmonary tuberculosis; dilated aortic valve; streptococcus septicæmia. *Pancreas:*—Not remarkable. Mic.:—No sclerosis of parenchyma; rich infiltration of lymphoid cells. Considerable fat tissue. Arteries thickened. Many of the islands show hyaline degeneration.

Case LV. Mass. Gen'l Hosp. 839, f., 53 yrs. U. S. Duration of diabetes 9 mos. Glucose, acetone and diacetic acid in urine. Died in coma a few days after admission. Anat. Diag.:—Diabetes; pneumonia; fibromyoma of uterus; chronic peritonitis; streptococcus infection. *Pancreas:*—Of fair size. On section, normal. Mic.:—Mild interacinar pancreatitis, unevenly distributed. Lymphoid and plasma cells are collected in some places. Vessels slightly thickened. Slight thickening of insular capillaries.

Case LVI. Mass. Gen'l Hosp. 1050, f., 70 yrs. Gave history of attacks of angioma. Unconscious when admitted to hospital. Glucose 3.5%; no acidosis. Anat. Diag.:—Diabetes; obsolete tuberculosis of lungs; senile kidney and liver; fatty heart; aortic sclerosis. *Pancreas:*—Normal. Mic.:—Parenchyma normal. Arteries thickened and hyaline. Islands show considerable thickening of capsules and insular capillaries.

Case LVII. Mass. Gen'l Hosp. 1094, m., 20 yrs. U. S. Polyuria for 3 wks. Disease ran acute course. Sugar 5%; acetone present; no diacetic acid. Died in coma. Anat. Diag.:—Diabetes. *Pancreas:*—Small and soft. Mic.:—Normal pancreas. Islands, however, are rather scarce and small, none being found over 200 microns in diam.

Case LVIII. Mass. Gen'l Hosp. 1202, m., 60 yrs. Eng. Duration 4 wks. Died in coma second day after admission. Glucose 2%; acetone and diacetic acid present. An acute, severe case. Anat. Diag.:—Diabetes; arteriosclerosis; gangrene of foot; chronic appendicitis; acute degeneration of kidneys. *Pancreas:*—Rather small, otherwise normal. Mic.:—Advanced interacinar sclerosis; considerable infiltration of lymphoid, polymorphonuclear and eosinophile cells; arteries thickened. Acini atrophic in places. Number of islands very small. Islands show considerable sclerosis.

Case LIX. Mass. Gen'l Hosp. 1358, m., 45 yrs. Irish. Admitted unconscious. Glucose 3%; acetone marked. Slight diacetic acid. Anat. Diag.:—Diabetes; chronic interstitial hepatitis with siderosis. Chronic interstitial pancreatitis; acute degeneration of kidneys; obsolete tuberculosis of bronchial gland. *Pancreas:*—Soft, dark brown color. Ducts normal. Mic.:—Marked new growth of connective tissue between the acini. Lobules widely separated by adipose tissue. Universal deposition of iron-containing pigment. Many acinar cells loaded with pigment. Arteries thickened. Infiltration of polymorphonuclear and lymphoid cells about larger ducts. Islands normal in size and number; many of them are surrounded by dense capsules of fibrous tissue; insular capillaries sclerosed. Many insular cells loaded with pigment.

Case LX. Mass. Gen'l Hosp. 1493, f., 48 yrs. Italian. Glucose 4.8%; acetone and diacetic acid present. Died without coma 10 days after admission. Anat. Diag.:—Diabetes, gangrene of arm, arteriosclerosis, slight hyperplasia of spleen, syphilitic (?) hepatitis. *Pancreas:*—Rather small; on section normal; duct free. Mic.:—Moderate grade of interacinar pancreatitis. Scattered groups of lymphoid and plasma cells. Vessels thickened; considerable fat tissue. Islands numerous, and show well-marked sclerosis; most of the islands have suffered severe hyaline changes.

Case LXI. Mass. Gen'l Hosp. 1595, f., 56 yrs. U. S. Duration of diabetes 15 yrs. General health excellent. Last two years on strict diet. Admitted last time for pneumonia, with glucose 1.2% (had never been over 2%). No acidosis. Died with pneumonia. No coma. Anat. Diag.:—Diabetes; pneumonia; arteriosclerosis; hypertrophy and dilatation of heart; muscular atrophy. *Pancreas:*—Normal, duct free. Mic.:—Well-marked increase of interacinar tissue in places. Considerable infiltration of lymphoid, plasma and eosinophile cells. Vessels thickened. Islands markedly sclerotic.

Case LXII. Mass. Gen'l Hosp. 1643, m., 59 yrs. U. S. Never sick before admission. For three weeks food has caused distress, vomiting, etc. Operation, coma, death. Glucose 2.2%. Anat. Diag.:—Diabetes; duodenal ulcer; operation wound; peritonitis. *Pancreas:*—Rather small, two-thirds usual volume. Tissue tough in places. Duct free. Mic.:—Well-marked interlobular and interacinar sclerosis; rich infiltration of lymphoid and plasma cells. Arteries slightly thickened. Islands very scarce; some of them show well-marked sclerosis and infiltration of lymphoid cells.

Case LXIII. Mass. Gen'l Hosp. 1770, f., 39 yrs. Negro. Polyuria for 4 yrs. Considerable loss of weight during last few weeks. Glucose 6.5%; acetone and diacetic acid present. Died in coma. Anat. Diag.:—Diabetes; gangrene of foot; chronic endocarditis; arteriosclerosis; myomata of uterus. *Pancreas:*—Normal, duct free. Mic.:—Moderate interacinar sclerosis. Arteries thickened. A few pink-staining acini. Islands very scarce, and rather small. Island cells small and pyknotic. Insular capsules and capillaries thickened.

Case LXIV. Mass. Gen'l Hosp. 1855, m., 60 yrs. U. S. Duration uncertain from history. Died 4 days after admission without coma. Glucose 4.8%; slight acetone and diacetic acid. Anat. Diag.:—Diabetes; septic endocarditis; cardiac hypertrophy; chronic cholecystitis; obsolete tuberculosis of lungs; streptococcus septicæmia. *Pancreas:*—Normal. Mic.:—Parenchyma normal. Arteries thickened. Considerable fatty infiltration. Islands scarce; insular capillaries thickened and capsules sclerotic. Some of the islands are hyaline.

Case LXV. Mass. Gen'l Hosp. 1890, f., 60 yrs. U. S. Symptoms for 4 or 5 mos. Glucose, acetone and diacetic acid present. Died in coma. Anat. Diag.:—Diabetes; arteriosclerosis; chronic endocarditis; gall-stones; obsolete tuberculosis of lungs; myoma uteri; fatty liver. *Pancreas:*—Quite small. On section normal. Duct free. Mic.:—Considerable interacinar sclerosis; many scattered groups of lymphoid cells. Considerable fatty infiltration. Arteries thickened. Islands are infiltrated by lymphoid cells in some instances, and show considerable sclerosis.

Case LXVI. Mass. Gen'l Hosp. 1891, m., 30 yrs. U. S. Duration of diabetes 2 yrs. Glucose 2.9%. Slight acetone and diacetic acid. Died in coma. Anat. Diag.:—Diabetes; pneumonia; focal necrosis of pancreas; old tuberculosis of lung; fatty liver. *Pancreas:*—Macroscopically normal. Duct free. Mic.:—Moderate interacinar pancreatitis, unevenly distributed; considerable infiltration of lymphoid and plasma cells; suppurative inflammation about ducts. Number of islands quite small. They show slight sclerosis; many are infiltrated by a considerable number of lymphoid cells.

Case LXVII. Mass. Gen'l Hosp. 1909, f., 68 yrs. U. S. Polyuria for 5 or 6 yrs. No other symptoms of diabetes. Glucose 5%; acetone and diacetic acid present. Died in coma. Anat. Diag.:—Diabetes; arteriosclerosis; gangrene of foot; fat necrosis; fatty liver. *Pancreas:*—Large; fat necrosis on surface. Cut surface normal. Mic:—Considerable interacinar sclerosis, with abundant infiltration of lymphoid and plasma cells. Arteries thickened and hyaline. Islands numerous, large (some 550 microns in diam.) and considerably sclerosed. Severe hyaline changes in many islands.

Case LXVIII. Mass. Gen'l Hosp. 1917, m., 52 yrs. U. S. Polyuria for a year. No other symptoms of diabetes. Digestive disorders. Died in coma. Glucose 7%; acetone and diacetic acid present. Anat. Diag.:—Diabetes; arteriosclerosis; gangrene of toe; streptococcus septicæmia. *Pancreas:*—Appears normal. Ducts free. Mic.:—Slight increase of interacinar stroma in places. Considerable fatty infiltration. Arteries thickened. A few pink-staining acini. Islands numerous, and large (some 500 microns in diam.). Islands show well-marked sclerosis, and most of them have suffered some hyaline changes.

Case LXIX. Mass. Gen'l Hosp. 2047, m., 31 yrs. Irish. Duration of diabetes 5 yrs. Died in coma. Glucose, acetone and diacetic acid present. Anat. Diag.:—Diabetes; chronic peritonitis and appendicitis; acute degeneration of kidneys; focal pneumonia; hypoplasia of heart. *Pancreas:*—Appears normal. Mic.:—Well-marked interacinar pancreatitis; infiltration of lymphoid and plasma cells. Arteries slightly thickened. Number of islands very small; they show well-marked sclerosis of the capsule and capillaries,

Case LXX. Boston City Hosp. 73, '08, m., 27 yrs. Irish. No history obtained. Diabetes extremely severe. Glucose and acetone present. Died in coma. Anat. Diag.:—Diabetes; arteriosclerosis; chronic pleuritis; hæmangioma; congestion of viscera. *Pancreas:*—No gross lesions. Mic.:—No sclerosis of parenchyma; no infiltration. Arteries slightly (?) thickened. Islands very scanty and very small (100–125 microns in diam.). Island capillaries not appreciably thickened.

Case LXXI. Boston City Hosp. 164, '02, m., 43 yrs. U. S. Duration of diabetes 2 yrs. Failed rapidly during last 8 mos. Lost 40 lbs. Glucose 1.25%; acetone and diacetic acid present. Died in coma. Anat. Diag.:—Diabetes; pneumonia; pulmonary tuberculosis. *Pancreas:*—Usual size; lobules gray, firm and very distinct; very little fat. Interlobular tissue lax. Mic.:—No sclerosis of parenchyma, vessels not appreciably thickened. Islands are large and numerous (some of them 500 microns in diam.). They all show a very marked hyaline degeneration.

Case LXXII. Boston City Hosp. 82, '07, f., 59 yrs. Duration of diabetes 6 yrs. Admitted comatose. Glucose 6.25%; acetone and diacetic acid present. Anat. Diag.:—Diabetes; pelvic peritonitis; cholelithiasis; chronic cholecystitis; arteriosclerosis; myomata uteri; chronic endometritis. *Pancreas:*—Considerable fatty infiltration. Pancreatic tissue firm. No gross lesions. Mic:—Well-marked interacinar pancreatitis. Moderate infiltration of lymphoid cells. Arteries thickened. Islands quite large, some measuring 500 microns in diam. Considerable sclerosis of islands; a number of the islands show hyaline degeneration.

CASE LXXIII. Boston City Hosp. 20, '99, f., 9 yrs. Duration of diabetes 5 mos. Glu ose 6.6%. *Pancreas:*—Microscopically shows no interstitial sclerosis. Arteries normal. Islands normal.

CASE LXXIV. Long Island Hosp. 7186, m., 12 yrs. Duration of diabetes 1 yr. Glucose 5%; acetone and diacetic acid present. *Pancreas:*—Microscopically normal in every respect, except for marked hyaline degeneration in a considerable number of the islands.

CASE LXXV. Penn. Hosp. 785, f., 57 yrs. Negro. Duration of diabetes 2 yrs. 137 gms. glucose in 24 hours; much acetone. Died in coma. Anat. Diag.:—Diabetes; broncho-pneumonia; colloid goitre with areas of calcification; chronic perihepatitis and splenitis; scars of left kidney; fatty degeneration of kidneys; infantile uterus. *Pancreas:*—25 cm. in length. Of medium size, decreased in consistency; ampulla of Vater patulous; duct clear. On section, pinkish and shows moderate lobulation. Mic.:—Well-marked interacinar pancreatitis. Arteries thickened and hyaline. A few pink-staining acini are found. Islands very scarce. The few which are found show moderate increase of fibrous tissue.

CASE LXXVI. Penn. Hosp. 938, f., 70 yrs. Irish. Duration of diabetes 4 yrs. (?). Severe illness of only a few days' duration. Large amount of glucose in urine. Died in coma. Anat. Diag.:—Diabetes; marked arteriosclerosis; chronic nephritis; chronic cholecystitis; cholelithiasis; cardiac hypertrophy; fatty heart and kidneys; latent tuberculosis in both lungs; ulcer of ileum; chronic interstitial pancreatitis with degeneration of the islands of Langerhans. *Pancreas:*—Wt. 90 gms. Quite small and hard; duct patent. On section appears normal. Mic.:—Definite interacinar pancreatitis. Considerable infiltration of lymphoid, plasma and eosinophile cells. Arteries thickened. Islands quite large, some measuring 600 microns in diam. Nearly all of them show severe hyaline degeneration.

CASE LXXVII. Penn. Hosp. 608, f., 36 yrs. U. S. Paresis of legs for 18 yrs. Admitted unconscious. Large amount of glucose in urine; acetone present; no diacetic acid. Died in coma. Anat. Diag.:—Thrombosis of auricular appendages, abdominal aorta and branches from renal arteries downward; multiple anæmic infarcts of spleen and kidneys; fatty degeneration of heart, liver and kidneys; acute nephritis; broncho-pneumonia; cholelithiasis. *Pancreas:*—Wt. 90 gms. 18 cm. in length; fairly firm; on section grayish. Duct of Wirsung patent. Duct of Santorini closed. Mic.:—Moderate interacinar pancreatitis, unevenly distributed. Arteries slightly thickened. Islands large, some 450 microns in diam. The insular capillaries are moderately thickened. Some of the insular cells show mitotic figures.

CASE LXXVIII. N. Y. City Hosp. D., f., 50 yrs. Can. Had no knowledge of diabetes until gangrene of foot set in. Duration of diabetes 9 mos. in hospital. Glucose 4½%; acetone present; diacetic acid absent. Anat. Diag.:—Thrombotic softening of left internal capsule; gangrene of foot; arteriosclerosis; fatty heart; broncho-pneumonia; chronic nephritis; fatty liver. *Pancreas:*—Short, small, surrounded by fat. Lobules white and separated by great quantities of fat. Cut surface presents same picture. Mic.:—Very marked and universal invasion of fat tissue; parenchyma reduced in amount; lobules and acini pressed apart. Arteries thickened and hyaline. Islands numerous and large (some 600 microns in diam.). Islands sclerotic, some hyaline.

Case LXXIX. N. Y. City Hosp. Schr., m., 69 yrs. U. S. Glucose 3.4%; acetone present; no diacetic acid. Cause of death was infection following operation. Anat. Diag.:—Diabetes; arteriosclerosis; fractured humerus; cardiac hypertrophy; chronic myocarditis; chronic nephritis; chronic parenchymatous degeneration of liver. *Pancreas:*—Head thick, body thin. Considerable superficial fat. Hemorrhagic streaks; cut surface pale and infiltrated with fat. Lobulations not well marked. Mic.:—Considerable interacinar sclerosis. Abundant fat infiltration. Arteries thickened and hyaline. Acini atrophic in places. Islands show well-marked sclerosis.

Case LXXX. N. Y. City Hosp. Nes., f., 65 yrs. U. S. Glucose present. No history. Anat. Diag.:—Diabetes; softening of right internal capsule; atrophy of heart; chronic nephritis; arteriosclerosis; fatty cirrhosis of liver; pneumonia; myomata of uterus. *Pancreas:*—Small, wt. 100 gms.; 17 x 5 x 3 cm. Appears firm when cut. Lobules separated by fat; much connective tissue about duct. Mic.:—Well-marked interacinar pancreatitis; moderate infiltration of lymphoid cells. Considerable fatty infiltration. Arteries thickened. Islands very scarce, and of small size (100–225 microns in diam.). Considerable sclerosis of islands.

Case LXXXI. N. Y. City Hosp. Fis., m., 56 yrs. Glucose 0.75%. Operated on for gangrene of leg; infection; death. Anat. Diag.:—Diabetes; gangrene of leg; arteriosclerosis; atrophy of adrenals; fatty liver; degeneration of heart. *Pancreas:*—Large, long, flat. On section appears normal. Mic.:—Great increase of the interacinar connective tissue. Considerable infiltration of lymphoid and plasma cells. Arteries thickened. Many acini atrophic. Number of islands small. Marked insular sclerosis.

Case LXXXII. N. Y. City Hosp. Mar., m., 47 yrs. Fairly acute onset of diabetes, duration 1 yr.; loss of wt. 90 lbs. Glucose 3.75%; acetone and diacetic acid present. Died in coma. Anat. Diag:—Diabetes; arteriosclerosis; hypertrophy of heart; chronic nephritis; chronic splenitis; latent pulmonary tuberculosis; perinephritic abscess. *Pancreas:*—Narrow; well-separated lobules, quite firm and rough; atrophic parenchyma with considerable fibrous growth between lobules. Mic.:—Moderate interacinar pancreatitis. Vessels thickened and hyaline. Considerable post-mortem autolysis. Islands show well marked sclerosis.

Case LXXXIII. N. Y. City Hosp. Con., m., 60 yrs. German. Duration of diabetes 3¾ years. Lost 35 lbs. in last 2 yrs. Onset was gradual. Glucose 2%; acetone present; no diacetic acid. Cause of death was tuberculosis. Anat. Diag.:—Diabetes; arteriosclerosis; calcified pituitary gland; acute diffuse miliary tuberculosis of lungs; tuberculous pleurisy; atrophy of heart. *Pancreas:*—Small, 15 cm. long, and 3.5 cm. broad in middle part. Mic.:—Well-marked interacinar sclerosis, severe in places. Arteries thickened and hyaline. Number and area of islands very small. Moderate sclerosis of islands.

Case LXXXIV. N. Y. City Hosp. Henn., f., 51 yrs. Irish. Patient admitted for infection in hand. Glucose 2%; no acidosis. Died in coma. Anat. Diag.:—Diabetes; gangrene of hand; arteriosclerosis; obesity; fatty liver; brown atrophy of heart; chronic splenitis. *Pancreas:*—Contains considerable adipose tissue. Arterial walls thickened. Mic.:—Great increase in interacinar stroma. Considerable fatty infiltration. Arteries thickened. Acini are atrophic in places. Marked sclerosis of islands; many hyaline islands in tail.

CASE LXXXV. Case of Dr. Stein. R. R., m., 43 yrs. Developed diabetes suddenly; 4% glucose; no acidosis. Glucose disappeared with diabetic diet; polyuria continued. Duration of disease 4 yrs. Died in coma. Towards last glucose dropped to 2 per cent. Acetone breath; *B*-oxybutyric acid in urine. Anat. Diag.:—Diabetes; chronic nephritis; fatty liver. *Pancreas:*—Small. Mic.:—Moderate interacinar pancreatitis. Rich infiltration of polymorphonuclear lymphoid and plasma cells. Suppurative inflammation in parts of the stroma. Arteries moderately thickened. Islands show considerable sclerosis.

CASE LXXXVI. Bellevue Hosp. 1163, m., 33 yrs. Admitted for acromegaly. Glycosuria (as high as 224 gms. in 24 hours) during 22 mos. Death, after a series of severe convulsions followed by coma and Cheyne-Stokes respiration. Anat. Diag.:—Acromegaly; diabetes; adenoma of pituitary body; persistent thymus; hyperplasia of the lingual and pharyngeal lymphadenoid tissue. *Pancreas:*—Large and firm. Wt. 170 gms. Lobulation distinct. No macroscopical lesions. Mic.:—No interstitial induration. Arteries somewhat thickened. Islands numerous, irregular in outline and larger than the normal (one measures 600 microns in diam.). Many islands show typical adenoma-like arrangement of their cells, which are columnar in type. The insular capillaries are thickened. A few of the islands are hyaline.

CASE LXXXVII. Bellevue Hosp. 1100, m., 73 yrs. German. In bad health for 6 mos. Admitted for carbuncles over scapula and in lumbar region. Glucose present. Died in coma. Anat. Diag.:—Diabetes; chronic pleuritis; chronic valvular disease; excised carbuncle. *Pancreas:*—Normal size, soft, rather pale. Presents no gross lesions. Mic.:—Moderate interacinar pancreatitis. Arteries thickened and hyaline. A few pink-staining acini. Islands show considerable sclerosis; a number are hyaline.

CASE LXXXVIII. Mt. Sinai Hosp. Nov. '08, m., 73 yrs. German. Diabetic symptoms were prominent. Died with toxæmia, following cystitis. Glucose 3.5%. No acidosis. Anat. Diag.:—Diabetes; chronic cystitis; ascending pyelo-nephritis; periprostatic abscess; arteriosclerosis. *Pancreas:*—Wt. 180 gms. Of good size, rather soft and covered with fat. On section, lobulation distinct. Considerable fatty infiltration in tail. Mic.:—Moderate interacinar sclerosis. Considerable infiltration of lymphoid and plasma cells. Adipose tissue abundant. Vessels thickened. Islands scarce; they show well-marked sclerosis and hyaline degeneration.

CASE LXXXIX. Boston City Hosp. 172, '05, m., 21 yrs. U.S. Admitted in coma. Considerable glucose in urine; acetone and diacetic acid present. Anat. Diag.:—Diabetes; incised wound of left arm; acute broncho-pneumonia. *Pancreas:*—Wt. 45 gms., normal in appearance. Mic.:—Free from sclerosis and inflammation. Islands normal in appearance. Contain some finely divided fat.

CASE XC. St. Luke's Hosp. No history obtained. *Pancreas:*—Microscopically moderate interacinar pancreatitis. Considerable infiltration of leucocytes and plasma cells, especially about the islands, which are sclerotic. Arteries normal.

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XI.

METABOLISM EXPERIMENTS IN ARTIFICIAL NUTRITION.

WITH SPECIAL REFERENCE TO THE HYPODERMIC METHOD.

By Herbert Swift Carter, M.D., Chief of Medical Clinic of the Dispensary.

(From the Pathological Laboratory of the Presbyterian Hospital and the Laboratory of Biological Chemistry of Columbia University, at the College of Physicians and Surgeons.)

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The whole subject of artificial nutrition presents great fascination for internists, both from the theoretical and the practical point of view; for the idea of nourishing the body, meeting its physiologic needs, so to speak, without the knowledge or consent of the patient, when occasion arises, has seemed an end highly desirable at times.

The conditions under which this would be of value are, of course, various, and need not be discussed here beyond pointing out the fact that in cases of subnutrition which, in part or whole; preclude the natural method of maintaining the physical economy, some such method would often be of the greatest use. Thus, it is indicated in acute gastroenteritis in children, in marasmus, in strictures of the alimentary tract when the patient comes under observation in a condition too weakened to allow of an operation for the time being, etc.

With the introduction of the stomach tube in 1870, by Kussmaul, we were enabled to nourish certain cases in which forced feeding is a necessity, despite the existence of a fairly normal digestive tract, as in cases of mental disease. Later, the rectum as an auxiliary stomach came into general use. Attempts were made to give nourishment by means of hypodermic food solution, or by the intraperitoneal route. Of course, any form of artificial feeding, to be entirely sufficient, has to meet the actual needs of metabolism. The requisite amount of nitrogen and heat units must be furnished or the organism will be forced to run at an economic loss, resulting in loss of flesh and strength.

Our knowledge of these requirements has been greatly increased since Voit and his pupils determined the average amount of the different food elements used by individuals doing light or heavy muscular work and maintaining their body weight. According to this standard, a person of average weight (70 to 75 kilos) needs about 118 grams of protein, 56 grams of fat and 500 grams of carbohydrate, with a total fuel value of 3,000 large calories, although Voit[1] was able to establish nitrogenous equilibrium for a short time in one patient who took only 8 grams of nitrogen, which corresponds to 48.5 grams of proteid, for a day's ration. This, however, he considered far too small an amount to maintain nitrogen equilibrium for any length of time.

Chittenden[2] became convinced that a low protein diet could be maintained, not only without detriment to the individual, but to his actual advantage, provided sufficient heat units were furnished by the other food elements. This he proved to his satisfaction in his interesting experiments on athletes, soldiers and students, representing individuals doing, respectively, severe, moderate, or light muscular work. He found that the average requirements per kilo of body weight were as follows: 0.12 gram nitrogen, representing 0.65 gram protein per kilo of body weight, with a total fuel value of the food represented by 32 calories per kilo, made up largely of fats and carbohydrates.

This, therefore, can be taken as representing the minimum food requirements necessary to maintain not only the nitrogenous equilibrium, but the general physical condition and body weight of persons who are at work, while at rest the calorific value of the food can be reduced to about 25 calories per kilo.[3] Any form of alimentation to be complete must meet these requirements, although under pathologic conditions one would be satisfied with something less than the ideal.

With the older standards, the problem seemed out of reach, but with the introduction of these lesser requirements artificial nutrition seems a much more promising field, and it was with this in mind that the following studies were undertaken.

In approaching this subject, two questions naturally present themselves: (1) Is the method ordinarily in use capable of accomplishing satisfactory artificial nutrition? (2) If not, wherein does it fail, and what other methods offer a possible solution of the difficulty?

In rectal feeding, the most common method of artificial nutrition, we have these questions to answer. As to whether this form of feeding is capable of supplying the needs of metabolism, if one regularly weighs these patients daily or even watches them clinically from day to day, the answer must be, No. They do not thrive. This, I think, will be borne out by the clinical experience of most of us. Rectal feeding is, at best, a poor substitute for stomach feeding, although, of course, patients differ, and in some it seems more successful than in others. It must be borne in mind, however, that most people can go without food very comfortably for a number of days, provided they are supplied with water, but after a certain time, whether on rectal feeding or not, they often seem to retrograde suddenly.

In order to answer the question as to the specific cause of failure in most of these cases, one must study the metabolism and carefully estimate the intake and output, with especial reference to the nitrogen, as the best index of metabolism. The following figures show the results of metabolism in three cases of rectal feeding and may be taken as fairly typical of a large class, as they occurred in one of the large city hospitals, under nursing conditions which are as good as can be found. If these results are true under favorable conditions what can be expected under ordinary conditions, outside the hospitals?

It can not be said that more satisfactory results may not at times be obtained by rectal feeding. But these cases probably represent the average. In all of them the usual precautions were taken: the colon was cleared daily, the injections were given high up, and the report, in every instance, was that they were "well retained." The entire twenty-four-hour urine, all results of rectal irrigation, and all stools were saved, and, together with a sample of the food, were sent to the laboratory daily. It seemed a work of supererogation to estimate the intake and output of nitrogen, for the results of the cleansing enemata were evidently an almost clear return of the nutrient material, and one could tell by inspection that little, if anything, was being absorbed. The following figures, however, represent the daily nitrogenous balances, estimated by the Kjeldahl method, and show graphically the failure of this method of nutrition; since in these cases, at least, nitrogenous equilibrium was far from being maintained.

CASE 1.—*Gastric Ulcer.* Man, aged 46, weight 115 pounds.

History.—Patient had been on rectal feeding three days before the test was begun. The nutrient fluid consisted of peptonized milk and eggs, 1240 c.c. per twenty-four hours, with a total nitrogen value of 11.78 grams.

NITROGENOUS BALANCE—FIRST DAY.

Total intake of food nitrogen	11.78 grams.
Total nitrogen output (urine, 4.74 grams; feces, 23.95 grams)	28.69 grams.
Total loss of nitrogen, 24 hours, output in excess of intake	16.91 grams.
Total loss in body weight	1 pound.

NITROGENOUS BALANCE—SECOND DAY.

Total intake of food nitrogen	12.40 grams.
Total nitrogen output (urine, 11.5 grams; feces, —; irrigation, 22.72 grams)	34.20 grams.
Total loss of nitrogen, 24 hours, output in excess of intake	21.80 grams.
Total loss in body weight	2 pounds.

NITROGENOUS BALANCE—THIRD DAY.

Food formula changed this day to peptonized milk, glucose and water, 2,000 c.c. in all for the twenty-four hours.

Total intake of food nitrogen........................ 7.20 grams.
Total nitrogen output (urine, 9.58 grams; feces, 6.43 grams) ....16.01 grams.
Total loss of nitrogen, 24 hours, output in excess of intake.. 8.81 grams.
Total loss in body weight........................... 2 pounds.

In this balance for the third day we see for the first time that something was actually absorbed by the rectum, or else retained, for the food intake was 7.20 grams nitrogen, and the fecal nitrogen equals 6.43 grams, leaving an absorption balance of + 0.77 gram nitrogen, which is, of course, so small as to amount to nothing from the standpoint of nutrition.

(NOTE.—The probable explanation of the fact that on the first two days the nitrogen in the stools and irrigations was greatly in excess of that artificially injected in the enemata is that material from previous days was retained and expelled along with the stools passed on test days.)

CASE 2.—*Gastric ulcer.* Man, aged 27.

Food: Peptonized milk and eggs.

NITROGENOUS BALANCE—FIRST DAY.

Total intake of food nitrogen........................ 6.37 grams.
Total nitrogen output (urine, 15.52 grams; feces, —; irrigation, 6.89 grams)..............................22.41 grams.
Total loss of nitrogen, 24 hours, output in excess of intake.16.04 grams.
(Patient could not be weighed.)

NITROGENOUS BALANCE—SECOND DAY.

Total intake of food nitrogen........................ 6.35 grams.
Total nitrogen output (urine, 15.60 grams; feces, 9.06 grams).....................................24.66 grams.
Total loss of nitrogen, 24 hours, output in excess of intake.18.31 grams.

CASE 3.—*Post-operative perforating gastric ulcer.* Man, aged 23.

Food formula, peptonized milk and egg, with panopeptone. Patient had been on this several days, when test was made only on one day, so that it is rather incomplete. Daily volume, 712 c.c.

Total intake of food nitrogen........................ 4.69 grams.
Total nitrogen output (urine, 19.04 grams; feces, 9.84 grams) ....28.88 grams.
Total loss of nitrogen, 24 hours, output in excess of intake 24.19 grams.

Little comment is needed in addition to a glance at the figures presented to prove the inadequacy of rectal feeding in these cases, and it may be assumed that in the vast majority of cases the results are little, if any, better.

The minus nitrogen balance varies from —8.81 grams to —24.19 grams, and is accompanied by a steady loss of weight in the first case (the only one weighed), apparently also in the others.

In a review of the literature on this subject, the only paper found to approach it from the standpoint of exact metabolism was by Edsall and Miller,[4] who investigated two cases with rather better results, so far as concerned actual absorption of the nutrient mixture of peptonized milk and eggs by the intestinal wall, but the nitrogenous loss averaged 11.8 to 70.9 grams nitrogen for the test period of six days. From clinical observation, however, and from the foregoing cases, the conclusion may be drawn with considerable certainty that rectal alimentation, as ordinarily practiced, is of little or no value in most instances, while in some it may prove harmful by using up the patient's strength. Of course it has been proved that water is well absorbed by the rectum and that this method of introducing water is of extreme value.

Having satisfied ourselves of the foregoing facts, the next question which naturally arises is: Can nutritive equilibrium be maintained more satisfactorily by any other artificial means?

Many investigations have been undertaken to determine the effect of intravenous injections of various foodstuffs in solution. Although the prime object of most of such attempts has been to study the effects of these substances on the organism, incidentally side lights have been thrown on the subject of nutrition, although mostly in a negative way, as substances so injected have been proved unsuitable for use in artificial nutrition, either because of their toxicity or because they are immediately excreted, for the most part.

Leaving out of consideration intra-peritoneal nutrition as unsuitable and impracticable for continued use, one naturally turns to the problem of artificial nutrition by the hypodermic injections of foodstuffs. With the introduction of Chittenden's lowered food requirements it occurred to the writer to attempt to prepare an artificial, soluble food, containing the precise nutritive requirements for an individual calculated on Chittenden's figures; to inject it into the subcutaneous tissue and determine the nitrogen balance day by day, to see if the requirements of the body were being met, and the body maintained, not only in nitrogenous equilibrium, but also in weight.

The literature on this subject is surprisingly scanty. There are no articles accessible to the writer in which the subject has been approached from the standpoint of metabolism. What has been done may roughly be divided into clinical inquiries and laboratory experimentation. The clinical observations have been of the crudest sort, and the reports contain almost no data concerning the cases or, at best, very insufficient data. Whittaker,[5] in 1877, reported the case of a man nourished for six days by subcutaneous injections of milk, extract of beef and later cod liver oil; but from the article there is no proof that the man was nourished in the real sense of the word, for no mention is made of body weight during this period, of the total amount of food injected, nor of the excretions, and we know that a patient can survive a short period of starvation with comparative ease. Kreng[6] injected 15 to 20 c.c. of olive oil hypodermically for twenty days and succeeded in maintaining the patient's weight (?) and strength.

Pick[7] quotes a case from Whittaker, who nourished a girl suffering from gastric ulcer, with a weak pulse and high temperature, for four days by hypodermic injections of milk and beef-blood, with "great increase in weight and strength, after which period the patient was able to take nourishment by mouth and the temperature fell." The dose of milk was a dram at a time, which is an absurdly small amount relative to the nutritional requirements, and makes one extremely skeptical of the results as recorded.

Leube[8] injected a 20 per cent. sugar solution and found that it was well borne if only a few cubic centimeters were given at a time, but the limit of absorption was 15 to 20 grams of sugar in the twenty-four hours, all beyond this being excreted in the urine.

A more recent report by Barker[9] speaks of the successful use of a 5 per cent. glucose solution in normal salt solution; this gives a solution which has the same freezing point as normal blood, —0.56° C. He used it in preparing some patients for operation, and only in one instance were the injections followed by glycosuria, although he fails to state the amounts injected, and gives no weight or metabolism data. This was tried on one case of marked asthenia from pyloric stenosis, but without success, as the patient died of exhaustion. On the other hand, most other experimenters agree that the usefulness of glucose is very slight, as it is so promptly excreted when given in nourishing amounts, while in the hands of some it has caused necrosis at the point of injection.

Turning to the purely experimental aspect of the subject, we find more data, but the results have been largely negative or unsatisfactory.

Of the substances tried, fat, in the form of oil or butter, has been most frequently used. Without going into the details of the various experiments, we may take Henderson and Crofutt's[10] statement as embodying the latest and most satisfactory results of experimentation along this line. They say: "Oil injected subcutaneously is readily and widely distributed through the subcutaneous tissue. It is not transformed *in situ* into adipose tissue. The tissues react to its presence as to any non-irritating, foreign substance. In the blood and lymph it does not appear in detectable amounts, and, while the oil is ultimately absorbed and utilized in metabolism, the process is one of extreme slowness. Oil injections in any moderate amount are, therefore, practically without nutritive value."

Winternitz[11] found that only 2 to 5 grams per day were utilized, and that for subcutaneous nourishment it was not of practical value.

When we come to consider the availability of protein for subcutaneous injection, we are met by a variety of opinions. Eichorn,[12] in a series of experiments, used cow's milk (⅓ water), "Sanders peptone" and egg albumin. He concluded (1) that they are wholly absorbed, (2) that egg albumin often leads to abscess formation, (3) that cow's milk, diluted, takes the longest time for absorption, (4) that there is no local reaction from 20 grams of peptone. He also injected five dogs with albumin, olive oil, cod liver oil, almond oil and sugar solution, and states that most of the dogs maintained their weight. Few details of the experiments are given and there are absolutely no metabolism figures; the whole subject is very incompletely treated.

In another series of experiments, he used defibrinated pigs' blood and calves' blood, but without satisfactory results, and concluded his article by saying: "When we look at the results of subcutaneous injection of foods, we can assume that materials which do not inflame the cellular tissue when injected can be used for a while, often to advantage, to save life or postpone death by starvation."

Leube[13] found that the injection of 18 grams of "somatose" into a dog caused marked disturbance of well-being and led to albuminuria, due to renal irritation (see also results of somatose injections in these experiments).

Ewald,[14] discussing the subject, dismisses with a word albumoses and peptones as poisonous and useless.

Leube,[15] in a later article, speaks much in the same way, but suggests that possibly albumin, in the form of an alkali albuminate or syntonin, might be of use, although he had not tried it (see second experiment in this series).

Four years ago Trolldenier[16] used an albuminous substance intermediate between the peptones and albumoses. Of this he gave 100 c.c. (10 per cent. solution) to each of several dogs. In summarizing his results he says that the dogs maintained their weight; that the urine showed albumose; that the injections were painful, and that abscesses developed at the point of injection.

It is hard to believe that these dogs could possibly have kept their weight on the amount of protein which Trolldenier gave them, as it has been found that a dog needs at least 0.3 gram nitrogen per kilo to maintain nitrogenous equilibrium, while these dogs received but a fraction of that, about 0.2 gram.

From this brief review of some of the most important contributions to the subject, it can readily be seen that the problem of providing sufficient food to an animal by injection, and at the same time approximately maintaining its nitrogenous equilibrium, to say nothing of its weight, is a most difficult one. It was felt, however, that it would be exceedingly desirable to attempt it, inasmuch as, if successful, some plan might be evolved for artificial nutrition in man, although any method to accomplish this successfully must be both clinically safe and nutritively sufficient, or nearly so, and must rest on the scientific facts of metabolism. Toward this end the following experiments were performed on dogs:

EXPERIMENTS ON DOGS.

Preparation of the Dogs.—As a routine, the dogs were put on the regular laboratory diet and confined in metabolism cages, where all excreta could be saved for analysis. As a rule, the dogs lost a little weight for a few days, and then settled down to almost constant weight from day to day. It was not until this had been accomplished that an experiment was attempted.

In the first attempt a food which was theoretically perfect was prepared from "somatose," representing the protein element in the form of soluble meat peptone, at the dog requirement of 0.3 gram nitrogen per kilo; the remaining requisite number of heat units (on human basis) being made up of glucose in normal salt solution, the whole being sterilized by thorough boiling.

EXPERIMENT 1.—Three preliminary injections were made of this food, the first representing 0.66 gram somatose per kilo, the other two 0.42 gram per kilo each, and the effects were noted. The larger amounts caused marked toxic symptoms, trembling, inability to stand, and rise of temperature, a trifle over 4° F. within four hours. The smaller amounts were better borne, but still gave rise to some toxemia. The urine after the third injection gave a positive biuret reaction, and sugar was also present, but apparently in small amount. After a few days of rest on regular mouth-feeding a forty-eight-hour period was begun with the same food, dividing the twenty-four-hour requirement into three injections for morning, afternoon and evening; at each injection an amount of peptone was used equal to 0.5 gram per kilo of weight.

Without going into the details of this experiment, it was seen that the dog showed less and less reaction, although the effects were too severe to constitute a result at all satisfactory from a clinical point of view. The temperature rose from 2° to 3° F., and the dog became weak and ill, the urine was lessened in amount, contained albumin, peptone, sugar, hyaline and granular casts. The injection fluid collected on the under side of the body and caused marked œdema. Between the 10 p. m. and the 10 a. m. feeding of the following day, the dog largely recovered its normal physical condition.

Following the period of injections, the dog passed an excessive amount of urine, probably from the subsidence of the œdema, and continued losing some weight, even after it had been on regular mouth feeding again, receiving daily the same amount of food that had maintained it previously at a practically stationary weight. This loss in weight continued for a few days, then the weight remained stationary at a lower level. This, curiously enough, was the rule after most of the injection experiments. These results were not such as were thought worth following up as the toxæmia was too marked, and for this reason chemical analyses were not made. Table 1 shows in graphic form the data collected.

TABLE 1.

Date.	Weight kilos.	Food Solution. c.c.	Volume Urine. c c.	Urine. Sp. Gr.	Clinical Notes.
1. March 30...	6.43	†	340	1016	Dog well.
2.* March 31...	6.66	315	138	1045	Dog weak; some difficulty in standing. Temperature 104.5° F. Œdema.
3.* April 1.....	6.70	315	160	1043	Has had six injections; condition about same; urine contains albumin, peptone, sugar, hyaline and granular casts.
4. April 2.....	6.03	†	705	1011	Dog fairly well again.
5. April 3.....	5.86	†	390	1014	Urine; albumin, distinct trace; sugar absent, occasional cast.

* Injection period. † Regular food.

Experiment 2.—In the second experiment it was thought that possibly an alkali albuminate made from meat would meet the essential qualities of solubility and being capable of sterilization, and might also be found to be less toxic than the peptone; this was prepared and diluted with normal salt solution. No account was taken in this experiment of furnishing the required calories, as it was undertaken solely with the view of seeing whether or not such a preparation would be of use.

The results of the injection of the alkali albuminate were most unsatisfactory, causing vomiting, bloody diarrhea, renal irritation, and local necrosis at points of injection.

The meat peptone and albuminate having proved so unsatisfactory, it was thought that possibly the peptone from cow's milk might be better borne, for it was conceivable that some of the toxicity of the meat peptone preparations might have been due to the extractives present.

In order to make this milk peptone, the certified city milk was used, after removing the gravity cream (as we have seen the fats are so slowly and insufficiently absorbed); this was then digested for three hours, by means of dry extract of pancreas with dilute sodium carbonate. The liquid was then sterilized by boiling, strained and put in sterile flasks after removing a sample for nitrogen determination.

Experiment 3.—For this experiment a small, pregnant dog, weighing 5.19 kilos, was used, and in order to find out at once the toxicity of this milk peptone, rather large amounts were used, equivalent to 0.4 gram nitrogen per kilo, divided into two doses, given twelve hours apart. Following the first injection, the dog gave birth to one normal pup. There were only moderate toxic symptoms, nothing like as severe as those following beef peptone and albuminate. Although the results with the milk peptone were not entirely satisfactory, it was decided to go ahead, employing a three-day period with this large amount of protein injection. The reason for using so much more than the absolute dog requirement was to determine whether or not it was dangerously toxic, this percentage of nitrogen per kilo being nearly four times that required for man.

In spite of this, it will be seen that the mother lost weight decidedly, and after the first day the temperature rose 2° F. and remained up. Some milk was secreted, but the pup failed to get sufficient nourishment and lost weight steadily. At the end of the third day, the mother was only in fair condition, was considerably poisoned, as evidenced by temperature, malaise and suffusion of conjunctivæ. The pup had lost in weight and strength, so it was decided to stop the experiment and return the mother to regular mouth feeding. This was done at the end of the third day, and although more milk began to be secreted, the pup was now too weak to get a supply, and died on the fifth day. After the first day, the mother refused all water by mouth, as she was evidently receiving sufficient fluid from the injections.

It will be seen on examining Table 2 from this case, that at the end of the first twenty-four hours the amount of urine excreted was smaller than normal (the usual occurrence in these cases), but of very high specific gravity, 1076 the first day and 1052 the second. These figures were much higher than any obtained throughout the entire series of experiments, and although no exact metabolism experiments were made, as the case was of too short duration and the conditions too exceptional to make it of value, the rate of metabolism was evidently excessive and was unquestionably a great factor in the safety of the animal, for the next two dogs, in one instance on the same and in the other on a smaller amount of nitrogen per kilo, died of toxæmia.

In trying to find a satisfactory explanation for this fact, viz., that this dog survived these injections, it was learned that Zachwegrwski[17] proved that in pregnant women there was antepartum nitrogen retention, and that postpartum there was a decided nitrogen loss, equilibrium not being established for four or five days, or even longer. He believed that the involution of the uterus caused the high nitrogen output accompanied by excessive nitrogen metabolism. It would certainly seem that this was the case, as the animal lost flesh out of proportion to the other animals, although it was on a higher percentage of nitrogen. So far as the pup is concerned, the method of hypodermic feeding of the mother failed to furnish the requisite amount of food, but as this was a very severe test for an artificial form of feeding, it is not surprising that it failed to meet these unusual demands.

TABLE 2.

Date.	Weight kilos.	Volume Urine. c. c.	Urine. Sp. Gr.	Food.	Clinical Notes.
1. July 29....	5.21	215	1020	Regular	Well and lively.
2. July 30....	5.14	295	1012	Regular	
3. July 31....	5.19	135	1020	Regular	
4.* Aug. 1....	5.12	115	1076	0.4 gr. N. per k. in peptonized milk.	Dog vomited. Rather weak; gave birth to pup. Weight of pup 21 grams.
5.* Aug. 2....	5.03	295	1052	"	Dog still weak. Pup weight, 18 grams.
6.* Aug. 3....	4.90	365	1031	"	Dog still weak. Pup weight, 17 grams.
7. Aug. 4....	4.38	515	1011	Regular	Dog better. Pup weaker; 16 grams.
8. Aug. 5....	4.40	210	1020	Regular	Pup weaker; 15 grams. (Died next day.)

* Injection periods.

Experiment 4.—In order to see whether the peptonized milk would prove as toxic under what might be termed normal conditions, another dog was injected with the same amount of nitrogen per kilo, namely 0.4 gram, divided into two doses daily. After the first injection, the toxic symptoms of the peptone were very evident, for the dog looked sick and could not rise. It received only three injections, at twelve-hour intervals, showing after each more and more evidence of toxæmia and dying twelve hours after the third injection.

The autopsy showed marked subcutaneous œdema on the flanks and under the belly; skin dark purple and ecchymotic. On section, this area of œdema was found infiltrated with bloody, serous fluid. The organs were sent to the Cornell Pathological Laboratory and the following report was received:

"*Liver.*—The whole section stains poorly. Many lobules show a marked degeneration as from a severe toxæmia. The ability of the cell body and nucleus to take on basic stain has been lost, indicating changes in the direction of degeneration, if not necrosis. The vascular elements seem normal.

"*Kidney.*—Tubules were in a condition of cloudy swelling and granular degeneration. Glomeruli, interstitial tissue, blood-vessels appear normal.

"*Heart and Spleen.*—Normal.

"*Intestines.*—Some congestion in spots; no hemorrhages."

Experiment 5.—The next trial to be recorded was with the peptonized skimmed milk, but peptonized only one hour and a half, as it was thought that possibly the length of the peptonization might make some difference in the degree of toxicity. Then instead of suddenly changing from all mouth feeding to all hypodermic feeding it was thought that it might be safer to make the change more gradually. The first day, three-quarters of the regular amount were given by mouth and one-quarter by hypodermic injection. The next day half mouth feeding and half hypodermic injection were resorted to, always on the basis of 0.3 gram nitrogen per kilo.

These injections caused some toxæmia from the first, but it was not until the second day that the dog looked really ill, and on the morning of the third day he was found dead, apparently from the same form of toxæmia as killed the preceding dog. The first day's injection represented 0.075 gram of nitrogen per kilo; the second day's, 0.15 gram of nitrogen per kilo.

The autopsy revealed local œdema with serous bloody fluid. The examination of liver and kidneys could not be completed in time, but on gross examination presented only slight evidences of cloudy swelling.

Although the outlook for accomplishing artificial nutrition with anything like exactness by the use of milk seemed most unpromising, it was felt that with milk as the most readily obtainable food, easy of preparation and sterilization, it would be worth giving it a final trial in the hope that some immunity to the poisonous effects might be acquired by using very small amounts at a time and increasing very gradually, waiting for all symptoms to subside before repeating the treatment.

Experiment 6.—The milk was skimmed and peptonized as in the last experiment, for one and a half hours, then sterilized. A 50 per cent. glucose solution was also prepared, in order to see how this would act in connection with the milk, thus furnishing some extra heat units.

A lively dog was obtained, put on the laboratory fare, weighed daily, and allowed to reach practically a stationary weight, which it did on a diet of 0.61 gram of nitrogen per kilo, although on this diet it put on 0.4 to 0.5 gram of nitrogen. A period of thirteen days was consumed in the experimental feeding, previous to which the dog, as has already been stated, was at an almost constant weight, although the nitrogen balance showed the 0.4 to 0.5 gram plus per day.

The injections were begun with very small amounts, *e. g.*, 0.098 gram of nitrogen per kilo, divided into two injections, and, as a rule, the amount was not increased for forty-eight hours. Including the two days on regular mouth feeding, preceding the experiment, and on all the thirteen days during which hypodermic nutrition was successfully maintained, the nitrogen balance was determined daily. While this always showed a minus balance, *i. e.*, the dog was excreting more nitrogen than it received in the food injected, still, with each increase in the amount of food the minus balance grew steadily less until on the tenth and eleventh days it was only 0.5 gram of nitrogen, the body weight remaining almost constant on those days. The food was then reduced and the minus nitrogen balance again increased to —2.62 grams. On increasing the food, it again sank to —0.311 gram on the fourteenth day.

These injections were given precisely as the others, twice daily, twelve hours apart, under aseptic precautions, and the animal showed surprisingly little reaction to them. During the earlier days of the injections, when the amount of nitrogen injected was low and the dog, of course, losing weight, he was not so lively, but was not ill; as the quantity of nitrogen was increased to 0.33 gram per kilo his general well-being improved and he was bright, lively and apparently normal. Up to the point of receiving 0.22 gram of nitrogen per kilo, there was no biuret reaction in the urine, showing that the peptone was being utilized completely. After this, there was always a slight reaction, increasing somewhat as the percentage of nitrogen was increased, although the dog's apparent well-being was improved and he seemed normal.

At times there was a trace of albumin in the urine, but never more; at no time were there casts. The sugar injected varied from nearly 4 grams per kilo per day to a little less than 1 gram, and varying amounts could always be detected in the urine. The lactose from the milk injections alone gave a moderate reduction of the copper, but not a quick, strong reaction, as when the glucose was injected. No accurate estimations of the amount of excreted sugar were made.

The dog's temperature at the beginning of the experiment was 103° F. (somewhat above normal), and never rose over 103.2° F. during the entire period of thirteen days. After the first two days, the dog was never thirsty and refused water during the last eleven days; it received more water by the injections than it really needed.

After the twenty-sixth (the last) injection on the thirteenth day of this experiment, the dog played about, ran to his cage, wagging his tail, showing a very nearly normal physical condition, except for the moderate loss in weight, 0.85 kilo. The loss of weight, which set in late in the experiment, probably shows that such a purely artificial form of nutrition can not be maintained indefinitely (Table 3).

SUMMARY.

In offering a short review of these experiments, the results may be stated in a few words as follows:

1. By the ordinary method of rectal alimentation it is practically impossible to nourish patients properly or to maintain nitrogenous equilibrium. There are probably few, if any, exceptions to this rule.

2. The hypodermic use of meat peptones and alkali albuminates is not feasible for artificial nutrition on account of their great toxicity and tendency to cause local necrosis.

3. Skimmed milk, peptonized one and one-half to three hours, may prove fatal if given hypodermically.

4. It was found possible to furnish a dog with full nitrogenous

TABLE 3.

Day	Weight in kilos	Volume of urine in c.c.	Sp. Gr. of urine	Chemical examination of urine			Total urinary N., grams	Food volume in c.c.	Total food N in gms.	Feces in gms.	Total fecal N in gms.	Nitrogen (gms.) in food per kilo of body weight	Total nitrogen balance	Remarks
				Albumin	Sugar	Biuret reaction								
1	6.60	230	1012	0	0	0	3.174	Reg.	4.034	39	0.458	0.61	+0.404 N	
2	6.55	255	1014	0	0	0	3.136	Reg.	4.034	25	0.320	0.61	+0.568 N	
3	6.68	145	1043	Trace.	+	0	4.364	135	0.656	0	0.	0.098	—3.708 N	Dog a little depressed.
4	6.50	395	1016	0	+	0	3.179	135	0.656	0	0.	0.1	—2.523 N	Dog better; lively.
5	6.31	220	1024	0	+	0	2.083	135	0.656	7	0.247	0.103	—1.674 N	Dog practically normal.
6	6.35	105+	1051	0	+	0	1.710	150	0.762	*	0.111	0.12	—1.059 N	Some urine contained feces, estimated as "liquid."
7	6.33	190+	1040	Trace.	+	0	2.622	150	0.762	*	0.287	0.12	—2.147 N	Some urine contained feces, estimated as "liquid."
8	6.30	210+	1040	Slight trace.	+	+	2.772	275	1.397	*	0.144	0.221	—1.524 N	Some urine contained feces, estimated as "liquid." First day with + biuret reaction.
9	6.25	255	1033	"	+	+	2.470	275	1.397	0	0.	0.223	—1.073 N	Dog apparently keeps well; not thirsty.
10	6.30	250	1038	"	+	Faint	2.292	373	2.100	0	0.313	0.333	—0.505 N	Very small minus balance.
11	6.31	260	1038	"	+	"	2.646	373	2.100	0	0.	0.332	—0.546 N	
12	6.10	335	1024	"	+	"	2.401	202	1.139	0	0.	0.186	—2.622 N	Dog continues all right.
13	5.95	240	1033	"	+	"	2.299	205	1.150	6	0.394	0.193	—1.543 N	
14	6.00	215	1049	"	+	"	2.401	373	2.092	0	0.	0.348	—0.311 N	Smallest minus nitrogenous balance.
15	5.75	415+	1033	"	+	"	3.577	373	2.162	0	0.	0.337	—1.640 N	Dog lively and well; trotted back to cage.

* Liquid.

requirements in the form of skimmed milk, peptonized one and one-half hours, and injected hypodermically in gradually increasing doses; when on the larger amounts of food the weight remained almost stationary, the nitrogenous balance showed only 0.3 to 0.5 gram loss, the dog being apparently physically in good condition.

5. For ordinary use, although successfully carried out in this instance, milk peptone, when injected hypodermically, must be considered dangerous, and until some method for avoiding the greater part of the natural toxicity of the product can be found, should not be used for nutritive purposes in man.

Since nutrition may be thus artificially carried out in dogs, it does not seem improbable that some modification of the method may be found that would be suitable for man, particularly as the minimum human nitrogen requirements are, per kilo, less than one-half that of the dog.

Addenda.—A subsequent attempt was made to nourish a dog on milk to which extract of pancreas had been added at the time of injection, in the hope that the process of peptonization would take place slowly in the tissues, thus reducing the tendency to toxic effects from large amounts of peptone. The experiment, however, was a failure, as the material caused wide local necrosis and made the dog exceedingly ill. It was then thought that possibly a dog might be immunized against this form of peptone, that serum from this animal might prove effectual in protecting another. The attempt was made, but, although the dog which it was attempted to immunize, showed a lessening reaction to the poisonous effects of the peptone, it never became immune. This, it was found, coincided with the experience of Friedman and Isaacs.[18]

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XII.

A STUDY OF CALCULUS LODGED IN THE URETER.

By Roland Hazen, M.D.

In reviewing the subject of calculus lodged in the ureter one is impressed by the scientific interest it affords and by the value to the clinician of being awake to the possibility of the occurrence of this condition.

In 1882 Bardenhaur[1] reported an operation in which a calculus was removed from the ureter. This is the first record to be found in literature of an operation for this condition, though it had long been known that calculi may remain impacted in the ureter, having been retained there in the course of their passage from the kidney to the bladder. Prior to this are recorded cases in which these calculi have been found on post-mortem examinations. As early as 1791 Chopart[2] described the clinical aspect of the migration of a calculus and the symptomatology of its arrested descent, with such a degree of accuracy, that little has since been added to our knowledge of the symptomatology. Rayer,[3] in 1837, noted the occurrence of multiple calculi in the ureter, which he termed "Chain Calculi."

Schenck,[4] in 1901, stated that the total number of cases in literature in which these calculi have been removed by operation is less than ninety, which figure will attest the usual text-book statements as to the rarity of this condition. In many of these cases the calculus was an unexpected finding at the time of the operation; and in others it had been diagnosed before operation, in which event it had usually been of a size and location that rendered it palpable through the abdomen, vagina, rectum or to the finger introduced through the urethra. The diagnosis, in fact, had rarely been made prior to the advent of the Roentgen Ray, except when the calculus was so situated that its presence was discovered by the palpating finger. The clinical manifestations are so characteristically insidious and ill defined that the symptoms frequently fail to suggest the possibility of the presence of these calculi, and it is very rarely that they assume sufficient definition to be positively diagnostic.

It is due to the added experience in the use of the Roentgen Ray in the detection of calculi that their presence in the ureter is found to be of far more frequent occurrence than had formerly been suspected. Leonard,[5] with his unequalled experience in this field of work, reported in 1901 the detection of one or more calculi in the ureter by means of the Roentgen method in nineteen cases. In 1902[6] the same author reported forty-seven cases, and in 1904[7] his total number of positive examinations had reached sixty-four. While a positive diagnosis cannot always be made from a Roentgen Ray examination, Leonard offers the following corroborative evidence in the sixty-four cases which he considered positive:

Fifteen were confirmed by finding a calculus at a subsequent operation.

Twenty-six subsequently passed calculi, after a course of expectant treatment, which was instituted as the result of the X-ray diagnosis.

Twenty-three were accompanied by symptoms not sufficiently grave to demand operative interference.

A very striking feature in this series of examinations is the ratio between the number of renal and ureteral calculi found. In three hundred and twenty Roentgen Ray examinations, thirty-three cases of renal and sixty-four cases of ureteral calculi were diagnosed. That is to say, the ureteral calculi were found twice as frequently as the renal. The finding of a calculus lodged in the ureter has always been looked upon if not as a condition of sufficient rarety to be styled a curiosity, at least as of far rarer occurrence than culculus of either the kidney or the bladder. The above ratio is probably higher than future surgical experience will verify, but with the more general recognition of the frequency of ureteral calculi as the underlying cause of many of the obscure disorders of the pelvic, iliac and lumbar regions, and with the greater frequency of X-ray examinations, including the pelvic portion of the ureter (which is the most frequent seat of these calculi), it is not improbable that this ratio will be found to be more nearly approximated than past experience has demonstrated.

The number of cases recorded in literature in which calculi have been removed from the ureter by operative intervention also shows a striking increase in the past few years. Schenck,[4] in 1901, reported that less than ninety such cases had been recorded in literature; while Tenney,[8] in 1904, refers to the records of one hundred and thirty-four cases, an increase within the past three years of forty-seven, which is more than half of the total number reported prior to that time.

In the ureter the calculi may be either primary or secondary: the primary variety is very rare and is formed by the deposit of phosphates or less frequently urates on the ureter wall about the site of an old ulceration or about a non-absorbable suture remaining after a previous operation. These calculi are very irregular and rough in outline, soft, porous and friable, and adhere tenaciously to the ureter wall. Their development is slow and progressive and they tend to remain quiescent.

The secondary calculi are those which form in the kidney and, entering the ureter, have become arrested in the course of their migration towards the bladder. They are more regular in outline and are usually round or oval. Uric acid calculi are the most common variety. Those composed of calcium are also frequent, while those composed of carbonates, phosphates and so forth, are more rarely encountered. Morris states that in some instances a soft, mortar-like, calculous mass is found.

In regard to sex, while renal calculi are found more frequently in the male the reverse seems to be true of the ureteral calculi. The ureteral cases in which sex is recorded in Tenney's series shows seventy-four females to fifty-eight males.

The various functional disturbances and pathological changes produced in the kidneys, ureter and bladder by the presence of a calculus in the ureter are dependent chiefly upon, first, the mechanical relations between the size, conformity and number of calculi and the anatomical characteristics of the ureter; second, the presence or absence of infection.

The diameter of the ureter is fairly uniform and when distended measures about 4.2 millimetres. There are, however, three recognized points at which the lumen is more or less constricted and thus serve as lodging places for calculi. The first is situated about seven centimetres from the beginning of the ureter. The second, which is not constant, being present in about three-fifths of the cadavers examined by Tanquary,[9] is located near the pelvic brim as the ureter crosses the common iliac artery. The third is at the entrance of the ureter into the bladder.

The nerve supply[10] of the ureter is of interest as explaning certain points in the symptomatology. Those of the upper portion of the ureter and kidney are supplied by the renal plexus, the middle by the spermatic plexus, and the lower portion and the bladder by the hypogastric plexus. The renal plexus is formed by branches from the solar and aortic plexuses and is situated at the hilum of the kidney. The aortic plexus also enters largely into the formation of the spermatic and hypogastric plexuses and thus serves as a central connection between the kidney, ureter and bladder. The kidney and upper portion of the ureter, through the renal plexus, are closely associated and are in direct communication with the great visceral centre, the solar plexus. While the lower portion of the ureter and bladder, though more remotely connected with the solar plexus, are more or less intimately associated with each other.

A calculus having entered the ureter from the kidney may pass through one of several series of events.

1. Exceptionally a small, smooth stone may pass down the entire length of the ureter and into the bladder without causing any subjective symptoms.

2. A larger stone, on entering the ureter, may call forth an acute attack of pain located in the lumbar region, appearing suddenly in a previously healthy person, radiating down the course of the ureter and associated with nausea, vomiting and faintness. The calculus may then return again into the pelvis of the kidney, there to remain for months or years without causing evidence of its retention.

3. More commonly the proportionate size of the calculus, as compared with that of the lumen of the ureter, is such as to permit of a gradual descent of the calculus, being propelled onward by the pressure of the urine upon it. The length of time elapsing between its entrance into the ureter and its exit into the bladder, and the acuteness and severity of the symptoms, present a wide range of variation, depending upon: the power of the propelling force or the secretory activity of the kidney, which is usually inhibited to a greater or less extent; the degree of resistance offered through the disproportion between the size of the calculus and the normal lumen of the ureter; or upon the amount of congestive thickening due to trauma inflicted upon the walls of the ureter through the irregularity and the roughness of the calculus.

4. A calculus, in the course of migration, with its accompanying paroxysms as above, may become indefinitely arrested at any point in the course of the ureter, though usually at one of the three natural points of constriction, with a prolongation of the symptoms in lessening severity.

5. Frequently a calculus may pass through a portion of the ureter unnoticed when the first evidence of its presence is to be found in the symptoms referable to its impaction in the ureter.

The impaction of a calculus in the ureter is brought about, according to Morris,[11] by its size or the irregularity of its surface, setting up a congestion of the mucous membrane of the ureter. Should the irritation lead to thickening, rigidity or stenosis at the seat of the impaction, the stone remains permanently fixed. The spasm produced in the ureter by the presence of this foreign body is also looked upon as a potent factor in causing its detention.

The form of a calculus thus lodged in the ureter presents many interesting and curious features as the result of its adaptation to its surrounding conditions during the course of its subsequent development. The original rounded form as it descends from the pelvis of the kidney may be more or less perfectly preserved during its sojourn in the ureter; but more characteristic, especially after a long period of detention, is the finding of an oval, elongated calculus. As described by Kelly[12] the length of these calculi is four to six times the diameter, which averages five millimetres, and they are pointed at both ends. Their form and the appearance of the layers show that they gain by accretion at the ends and lose by attrition at the sides. They occasionally present a groove at the side for the passage of the urine, may be T or X shaped when partly in the ureter and partly in the renal pelvis, or horse-shoe shape, as in the case of R. B. Hall's, where the calculus produced an intermittent flush-tank, hydro-nephrosis.

In size they seldom exceed one by two centimetres, though occasionally much larger proportions are attained. Israel[13] reports a case in which the calculus measured seventeen centimetres long by nine centimetres in circumference.

A person who has developed a calculus may be considered as predisposed to the further formation of calculi, whether this tendency be primarily due to the composition of the urine secreted, to secondary changes produced in the urine through fermentation, or to certain pathological states of the mucous membrane lining the urinary passage. At all events multiple calculi of the ureter is a relatively frequent finding, and not infrequently are one or more calculi found in the opposite ureter, or in one or both kidneys.

In Schenck's[14] series of one hundred and one cases twelve contained more than one calculus on the same side. One case contained fourteen stones in one ureter, the largest being eleven by nine centimetres; another contained twenty-four stones tetrahedral in shape, and in another case eleven stones were removed through the urethra. Morris tells us that in some post mortem cases the ureter has been filled, or almost filled, from end to end with calculi.

The three points of constriction of the ureter above mentioned serve markedly as points of predilection for the lodgment of calculi. So commonly are calculi lodged in the immediate vicinity of one of these three points that the surgeon should regularly investigate each one of them, irrespective of any localizing symptoms present, which are often absolutely misleading. The relative frequency with which calculi are lodged at these different points is given by Schenck as the result of post-mortem and operative findings in the ninety-eight cases, as follows:

		Percentage.
1st.	Six centimetres from the kidney	20.4
2nd.	Near the pelvic brim, as the ureter crosses the iliac artery	14.5
3rd.	Within six centimetres of the entrance of the ureter into the bladder	56.1
4th.	All other places	10.0

Thus, according to this series, the vesical end of the ureter is the most frequent seat of arrested calculi. They are found here more frequently than in all other situations put together; and over two and a half times as frequently as at any other single location. Tenney, adding to Schenck's series, shows the location in one hundred and twenty-six cases to be practically the same as above, and also brings out the fact that the number of stones caught at these points corresponds to their relative degrees of constriction, the dimensions given below being practically agreed upon by Morris[15] and Robinson.[16] His figures for one hundred and twenty-six cases are as follows:

Location.	Diameter of Ureter. Millimeters.	No. of cases found	Percentage of cases found.
1. Seven centimetres below the pelvis of the kidney..	3.2	35	27.8
2. Just above or below the brim of the pelvis.......	4.0	18	14.2
3. As the ureter enters the bladder................	2.5	73	58.0

The calculus having lodged in the ureter pursues a variable course. It may be retained there, causing practically no disturbance of function or annoyance to the patient for an indefinite number of years; or it may be subsequently passed into the bladder without the patient having been apprised of its stay in the ureter. As long as it remains perfectly quiescent, and the interference to the flow of urine is neither marked nor of an intermittent character, and there is an absence of infection or inflammatory reaction, there will be little or no evidence of the presence of the calculus. Most frequently one or more of these conditions are not fulfilled, and we have a train of symptoms, usually characterized by their obscurity and lack of definition, though varying in severity with the degree of mobility of the calculus, the extent and character of its interferencc with the urinary flow, and the character of the inflammatory reaction in the urinary passages.

Hydro-nephrosis and hydro-ureter are frequently produced secondary to calculis of the ureter, depending for their development upon a continuously secreting kidney with an obstruction to the flow of urine, which is either incomplete, intermittent or of gradual development. As the detection of the condition of hydro-nephrosis is not readily accomplished, especially in its minor grades of development, it is not possible to formulate the frequency of its occurrence secondary to calculous obstruction of the ureter, though it may be inferred from the nature of events in the life history of this disease that the majority of the cases are accompanied by hydro-nephrosis to a greater or less extent at some time during their course. Conversely, in a certain percentage of cases of hydro-nephrosis, we may expect to find a calculus of the ureter as the cause. Morris states that Sir William Roberts, in thirty-two cases of hydro-nephrosis, found ureteral calculi in eleven, and Simon found seven out of eighteen cases to be due to this cause.

Occasionally a calculus is so lodged as to act as a ball valve in the ureter, producing an intermittent hydro-nephrosis. Leonard[5] reports that in three of his cases an intermittent flush-tank hydro-nephrosis from a partial occlusion of the ureter had lead to an original diagnosis of floating kidney. The knowledge of the presence of hydro-nephrosis is of prime importance in a prognostic and diagnostic bearing on the case. As it represents nature's effort to eliminate the stone through the natural passages it affords the only and a frequently efficient means of spontaneous cure. Through their frequent association we have, in hydro-nephrosis, therefore, a most valuable confirmatory evidence in suspected cases of calculus in the ureter. But, on account of the difficulty of its recognition, except when marked, it is not of frequent service in this connection. However, in Schenck's one hundred and one cases tumor of the flank was noted in nine. Possibly further refinement in the use of the Roentgen Ray will lead to a more frequent detection of this condition.

More important to the welfare of the patient is the ever existing danger of the stone becoming so situated as to suddenly and completely occlude the ureter, which occurrence may take place during the acute passage of a calculus, or by an impacted calculus on shifting its position. The outcome of this occurrence, if not relieved, will be either a functional death and atrophy of the kidney of the affected side, with resulting compensatory secretion of the opposite healthy kidney, or a sudden, complete bilateral anuria due to reflex, secretory inhibition of the opposite kidney.

In the former case the true condition may be totally unsuspected and the clinical picture may be nearly identical with that of the passage of the calculus as pointed out by Leonard[5] in the following contrast: If the calculus passes without detection the pain subsides after the colic, the urine clears up and perfect function returns, while, if the calculus becomes impacted in the ureter the anuria destroys the function of the kidney, the pain ceases, the urine from the other kidney is normal, and the "cure" is attributed to medication. That a sudden and complete stoppage of the ureter leads to a rapid atrophy and disappearence of the kidney has been demonstrated by observation and experiment.

The development of complete anuria of both sides evidently is dependent to a certain extent upon the portion of the ureter in which the calculus is lodged, as shown in a series of forty-seven cases collected by Morris, in which the locations were as follows:

Upper end of ureter	30 cases.
Middle of ureter	7 cases.
Lower end of ureter	10 cases.

This, as well as other recorded tables, indicates that the danger decreases as the calculus passes the upper constriction, and increases slightly as it reaches the lower constriction. The greater danger at the upper extremity is probably due, at least in part, to its more direct reflex communication with the opposite kidney through the renal and solar plexuses. Recovery from expulsion of the stone is considered as very infrequent by those who have written on this subject. Cabot[17] suggests that one of his cases recovered in this way, and Harrison cites a case in which there was suppression for fourteen days, followed by the passage of a calculus and subsequent recovery. Usually a fatal termination occurs at an earlier date if total anuria persists. Roberts gives the duration of life as from nine to eleven days, while Osler says that these cases may live ten days or two weeks.

From the steady pressure of a calculus against the ureter wall it may exceptionally ulcerate through into the peritoneal cavity, or into the retro-peritoneal space. The latter condition is reported in two cases in which a retro-peritoneal abscess was formed.

The presence of infection in varying severity is the rule when the condition has existed for some time and constitutes an additional menace to the life of the patient.

When the calculus is lodged near, or within, the vesical portion of the ureter, it may set up a violent cystitis, or the damming up of the infected urine by a calculus lodged in the lower part of the ureter may so lead to suppurative inflammation of the ureter above, the pelvis of the kidney, and the kidney structure proper, as to mask all suspicion of the calculous nature of the disease. In one hundred and thirty-three cases fifteen were operated upon for acute pyelitis or pyelo-nephrosis. A certain amount of inflammatory reaction at the seat of the stone is to be expected, producing a local ureteritis or peri-ureteritis, with the production of a varying amount of inflammatory exudate. This may be of material aid in diagnosis through the localized tenderness it affords, though the past records indicate that this tenderness has quite generally been mistaken for the more common inflammatory diseases of the other viscera lying in the neighborhood of the course of the ureter. In a number of cases the appendix, and more frequently an ovary, have been removed with but temporary relief, when a calculus was found in the ureter at a subsequent operation and its removal followed by complete recovery.

The symptomatology is rarely sufficient to make a positive diagnosis of calculus lodged in the ureter. Pain may be entirely absent but is more frequently dull and more or less constant, located usually in the pelvic or in the lumbar region, and at times it appears in exacerbations of increased severity, recurring at intervals of weeks or months. The recurrence of acute paroxysms almost invariably signifies that the calculus is changing its position. Radiation of the pain up or down the course of the ureter and to the groin from a point of greatest severity over the ureter, is present in the more acute paroxysms and is of diagnostic significance. The pain is probably most frequently noted in the lumbar region, often occurring simply as a dull, indefinite ache. Nausea and vomiting may accompany the acute paroxysms, and especially when the stone is located above the brim of the pelvis. Fever, malaise and headache, in a mild degree, though somewhat persistent, are present in some cases, evidently caused by the damming up in the ureter and pelvis of the kidney of purulent urine. Occasionally a chill is noted.

The differentiation from renal calculus is often impossible, and this constitutes probably the most frequent error in diagnosis, especially when the calculus is located above the brim of the pelvis. Morris says that the symptoms so resemble those of renal calculus that nine out of eleven cases of ureteral lithiasis were first operated upon with the conviction of finding kidney stones. When located near the brim of the pelvis the symptoms may be indistinguishable from those of appendicial origin or, in the female, from those of congestive or inflammatory conditions of the uterine adnexa. Contraction of the psoas muscle may be present when located in this region. The symptoms of cystitis, or those of calculus in the bladder, may be pronounced and constitute the only symptoms present, especially when the calculus is situated in the vesical end of the ureter, though tenesmus, frequent and painful micturition, may dominate the picture even when the stone is at a higher situation. Two such cases are recorded in which the stone was within one inch of the kidney.

The urine may be perfectly normal on the one hand, while on the other it may present practically the only signs of the presence of the calculus. Hematuria is the most constant finding and while repeated examinations may fail to reveal the presence of red blood corpuscles in the urine it is probable that there are very few cases which do not present a hematuria at some time during their course. The most favorable time for finding red blood cells is naturally after an attack in which the symptoms have been aggravated. Tuffier[19] considers that the presence of red blood corpuscles in the urine after physical exertion, in conjunction with the history of recurrent attacks of colic, is sufficient to diagnose the presence of a calculus situated above the bladder.

Pus in the urine is of too common occurrence in other conditions of the urinary tract to be of practical value in diagnosis. It may be present in varying quantities, or it may be entirely absent. However, the appearance of pus occurring intermittently in a urine that is normal at other times, and especially if its appearance is preceded or accompanied by an exaggeration of the symptoms referred to the region of the ureter, leads one to suspect a possible calculus origin.

Albuminuria is not an infrequent accompaniment of ureteral calculi, the explanation of which is to be found in the circulatory disturbance produced in the parenchyma of the kidney through the obstruction to the flow of urine or in the presence of pyuria.

The quantity of urine may not be altered; it may be voided in diminished amounts, depending upon the degree of obstruction and the state of the opposite kidney, or we may have it totally suppressed in the condition of calculous anuria. In the intermittent hydro-nephrosis, produced by a partial occlusion of the ureter, the quantity is diminished before and during an exacerbation of the symptoms following which a polyuria appears.

An aid to the diagnosis of urinary lithiasis may possibly be found in the further observations on the nitrogenous output in the urine, through its relation to the disposition of certain urines to form calculi. As a result of his experience in this field of research, Frederick E. Sondern[20] reports as follows: "In the chemical analysis of specimens of cases of renal stone, I was impressed years ago by an almost constant high relative as well as absolute nitrogenous output, and have come gradually to look upon this feature as an important point in differential diagnosis with almost constant success."

On physical examination a hydro-nephrotic kidney may be palpated when of sufficient size. The absence of rigidity of the abdominal muscles is of importance in the differentiation from the acute inflammations of the more superficially placed organs, with which this condition may readily be confused. Rigidity is practically never present except when suppurative changes have developed and are well advanced.

On careful, deep palpation valuable information may be gained by the finding of an area of tenderness well localized to some point in the course of the ureter. However, the tenderness may be so slight as to scarcely create a suspicion of the presence of a calculus.

The vaginal and rectal examinations are of service in detecting tenderness in the ureter when the calculus is situated in its lower portion, and in several cases calculi have been palpated and the diagnosis established in this way. The lower end of the ureter is frequently sensitive even when a calculus is located above the reach of the finger.

To palpate the ureter on vaginal examination the finger is directed upwards in the lateral fornix and then swept backwards, pressing firmly against the structures on the outer wall of the pelvis. A calculus can be palpated through the vagina if within two and a half inches of the bladder, according to Morris, and per rectum if within one and a half inches. Kelley states that a normal ureter is accessible per rectum all the way up to the pelvic brim.

Any one of the symptoms or signs of calculus impacted in the ureter may be produced by a variety of other conditions, and their grouping is so exceedingly variable that, with our present knowledge, it is impossible to outline a clinical picture that is either sufficiently definite or comprehensive to characterize this condition. However, both Schenck and Tenney have outlined the type of history in which a calculus in the ureter may be suspected. According to Schenck these calculi may be suspected if there is a history of repeated attacks of renal colic, occurring at intervals for years and, although the attacks have usually terminated with the passage of a calculus and the cessation of the symptoms, the last one ended more slowly and left behind a dull, aching pain with, possibly, tenderness somewhere along the course of the ureter. Tenney says that recurring attacks of colic, always referred to the same side, with pain radiating downward along the genito-urinary tract, accompanied by hematuria, with usually a diminished quantity of urine before and during the attack and an increased quantity after the attack, are the most reliable indications of a stone impacted somewhere between the kidney and the bladder.

The cystoscope and uretheral catheter afford a means by which the diagnosis can, in certain instances, be established. Through the cystoscope the presence of cystitis or a vesical caculus can be established or eliminated. A calculus protruding at the vesical orifice has been noted in several cases. The absence of the urinary flow from one side after an injection of methylene blue is easily detected and the appearance of a pouting and gaping ureteral orifice, surrounded by a congested area, indicates a lesion above in the affected ureter.

The ureteral catheter is of service in determining the relative quantities of urine passing through the two ureters and thus demonstrates the presence and degreee of any obstruction to the flow. If the catheter meets with an obstruction in the ureter its calculous nature may possibly be established by a method recommended by Kelly. A flexible catheter tipped with dental wax two parts, and olive oil one part, applied when hot and allowed to cool and harden, is passed into the ureter through an open-air cystoscope, with the patient in the knee-chest position. The wax, on coming in contact with the calculus, will receive the impressions of its rough surface, which are readily detected as scratch marks with the aid of a magnifying glass.

The X-ray, in competent hands, affords the most valuable means at our disposal for the detection of calculi in the ureter. In the diagnosis of pelvic shadows, however, several sources of error may be encountered, namely: calcified lymph nodes, phleboliths, calcified masses in the sacro-sciatic ligaments, calcified ovaries, calcified appendices, epiploicæ, and so forth. Leonard[21] states that in one case a phlebolith was found in the vaginal wall and in another case eight were found in the broad ligament. Brewer[22] encountered one case in which a calcified appendix epiploica, adherent to the ureter, was found at operation.

The treatment may be either expectant or operative. A small proportion of cases will pass these calculi after a course of drinking large quantities of water. Poland water has been recommended for this purpose, and it has also been recommended to supplement this treatment with massage along the course of the ureter. Leonard considers the presence of hydro-nephrosis as a direct indication for the expectant plan of treatment.

The great majority of cases, however, require operative intervention for their relief, immediate operation being called for when there is an associated complete bi-lateral anuria, or advanced suppurative condition of the kidney and ureter.

The lumbar incision is employed for calculi located at or above the brim of the pelvis, and, by its extension downward and inward above and parallel to Poupart's ligament, the pelvic portion of the ureter can be explored almost to the bladder. Other methods have been employed for reaching the pelvic portion of the ureter which are less mutilating. Of these the iliac route, which is practically identical with the operation for extra-peritoneal ligation of the common iliac artery, is the most generally useful. The vaginal route is useful in the female. The rectal route offers little inducement and great objection through the danger on infection. The perineal route and the posterior route, through an opening similar to Kraske's operation, and a pararectal route through the great sacro-sciatic ligament, have been suggested, though seldom used. The abdominal or trans-peritoneal route opens up the danger of infecting the peritoneum and does not provide for good drainage from the ureter. However, a median abdominal incision may be made for the purpose of exploration in doubtful cases, or for determining the exact condition of the ureter and position of the calculus, preliminary to an extra-peritoneal operation.

When the calculus is located in the vesical portion of the ureter it can best be reached from within the bladder through a suprapubic or a perineal incision, or through the dilated urethra. It is then extracted or expressed into the bladder, after dilating or splitting up the ureteral orifice if necessary.

In conclusion, the features of special interest which serve to commend this subject to our consideration, may be summarized as follows:

1. The increasing frequency with which the condition of calculus lodged in the ureter is being found.

2. The variation in the functional disturbances and pathological changes produced in the urinary tract, as the result of the presence of such calculi.

3. The frequency and accuracy with which the clinical picture may simulate that of other abdominal and pelvic lesions.

4. The ill defined nature and the variation in the grouping of the clinical manifestations.

5. The serious danger to health and life to which these patients are constantly subjected.

6. The dependence in establishing the diagnosis upon the recent methods of the Roentgen Ray, cystoscopic and ureteral examinations.

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XIII.

EXTRAPERITONEAL RUPTURE OF THE BLADDER WITH INTRAPERITONEAL TRANSUDATION OF URINE.

By Forbes Hawkes, M.D.

The following case is of interest on account of the paramount importance usually accorded to the differential diagnosis between extra and intraperitoneal rupture of the urinary bladder.

J. P., age 38 years, male, carpenter, brought into the Presbyterian Hospital, First Surgical Division, March 23rd, 1905, with the history of a fall in front of a trolley car that morning. It was said that the fender had rolled him over several times before the car could be stopped. When brought into the Hospital he was in great shock. Examination revealed a fracture of the pelvis (right pubic ramus), and multiple contusions. Some of these were marked over his right lower thoracic and iliocostal regions. Nine ounces of blood-tinged urine were withdrawn by catheter without difficulty. He was in no condition for surgical procedure on account of shock for about thirty-six hours. During this period he passed macroscopically clear urine, at times voluntarily, at times by catheter. There was microscopically a slight amount of blood in the urine. There was no difficulty in entering the bladder with a catheter. He gradually developed rigidity of both the recti and lateral abdominal muscles in their entire extent. The abdomen became distended, it was tympanitic over all except in the right flank, where there was some dullness. The supra-pubic region, especially on the right side, became gradually elevated and the superficial veins dilated. The scrotum became infiltrated, apparently with urine. He had no vomiting; he was constipated and passed no flatus. His temperature gradually rose to 102.4° F., his pulse to 96, respiration to 24. There was infiltration in the perineum. Diagnosis was made of peritonitis with probable rupture of the bladder and infiltration of urine. As soon as consent to operation was obtained (about fifty-six hours after the accident), exploratory laparotomy was done (Dr. Hawkes) just above the bladder. The following conditions existed:

The general peritoneal cavity contained a considerable amount of free blood-tinged fluid, with a slightly urinous odor. This was mostly sponged out, the remainder being caught on large pads introduced for this purpose. The patient was then put up in Trendelenburg posture and a hunt made for an intraperitoneal rupture of the bladder. The most careful search under excellent and very satisfactory illumination failed to reveal any rupture. The whole peritoneal plane, however, covering the bladder, and that part which is reflected on to the right anterior and lateral abdominal wall as far up as the right iliac fossa, was seen to be lifted up by the swollen cellular tissue underneath and small droplets of blood-stained urine were distinctly seen to ooze constantly through the peritoneum into the general peritoneal cavity. The exact rate of transudation was hard to calculate. It seemed as if about a drachm trickled through the part of the peritoneum exposed to view in the three to five minutes during which the observation lasted. The absence of any intraperitoneal rupture being ascertained, the abdominal wound was enlarged downwards over the seat of the fracture of the pelvis, and an extraperitoneal rupture of the bladder there found just under a comminuted fracture of the pubic bone, about an inch to the right of the symphysis. Through a catheter introduced into the urethra sterile salt solution was easily forced out through the bladder rent at this spot. After withdrawing the pads from the peritoneal cavity the peritoneum and abdominal wall were closed by layers, leaving in a small rubber tissue and gauze cigarette drain (no gauze projection from the lower end) for peritoneal drainage. This drain was made quite small because the examination of the urine passed during the forty-eight hours after his accident revealed no pus cells. A large rubber drainage tube was then placed down to the seat of the rupture in the anterior bladder wall (at the site of the pubic fracture) and sewed to the skin; gauze was lightly packed around it. The swollen scrotal tissues were incised in several places, liberating blood-tinged urine freely. The patient's general condition improved rapidly after the operation; the abdominal symptoms disappeared in about forty-eight hours. His convalescence was slow on account of his fractured pelvis. The bladder wound drained freely through the tube and surrounding gauze. Some of the urine, however, gravitated slowly into the gluteal region, forming a small collection there, which was opened under general anæsthesia about ten days later. Otherwise his convalescence was uninterrupted, the bladder wound healing by granulation and leaving only the comminuted fracture of the pelvis for further treatment. On April 9th, 1905, he started to void urine naturally and the function was soon restored. He left the Hospital on June 25th, 1905, with a small supra-pubic sinus leading down to the fractured area. He was able, at that time, to walk with assistance. The urinary function was then normal.

Remarks: The writer has not found such a case recorded in genito-urinary literature where urine was found in the general peritoneal cavity from such a source without an intraperitoneal rupture of the bladder. In this case the mechanical conditions were evidently as follows: the urine had been forced from the bladder by bladder contraction, through the rupture into the cellular tissues anterior to and to the right side of the organ; and these being over-distended, the urine was forced still further under pressure into the peritoneal cavity through the peritoneal meshes. In this case the rate of transudation of the urine through the peritoneal plane was probably greater after the peritoneal cavity was opened, than it had been at any time before, the counter pressure from intestinal distension being then removed. Whether in this case the peritoneum would have been able to take care of the presumably sterile urine which had accumulated there before the operation, had the exploratory opening into the peritoneum not been made and the rupture area in the bladder simply treated by drainage, is of course hard to say. That conditions somewhat similar to those disclosed by the order of operative procedure in this case may well have existed unrecognized in a number of the reported cases of extraperitoneal rupture of the bladder, seems not at all unlikely, the relative toxicity of the urine being one of the factors, perhaps, in the end result in such cases where the peritoneal cavity had not been opened.

XIV.

THE ASSOCIATION OF TUBERCULOSIS OF THE LUNGS WITH DIABETES MELLITUS.*

By Henry L. Shively, M.D., Physician in Charge of the
Tuberculosis Clinic.

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For two diseases so essentially different in their nature as are pulmonary tuberculosis and diabetes mellitus, there are certain points of analogy between them which are at once curious and striking. Diabetes is to be considered a typical example of a disease of metabolism, of disturbed function due to the action of unknown toxines originating within the body itself. The production of these toxines is apparently related in some way to the internal secretion of the islands of Langerhans, and there is accumulating evidence, for which we are largely indebted to the investigations of von Mering and Minkowski, and the recent researches of Hansemann, Opie, Herter, and Bosanquet, that the pathological basis of true diabetes is a congenital or acquired insufficiency of these histological elements of the pancreas. Hansemann found the pancreas diseased in seventy per cent. of all of his cases which came to autopsy. In nineteen cases Opie showed the gland to be affected in fifteen, Bosanquet in seventeen out of nineteen cases.

Tuberculosis of the lungs is perhaps the best known and most carefully studied example of a chronic, infectious disease due to a specific micro-organism introduced from without the body. Both diseases are usually progressive in their course and are regularly attended by emaciation; in both there is impairment of the power to utilize carbohydrate food; both diseases are very fatal in early life, and are, on the other hand, comparatively well withstood when they appear after middle age. Both have strong racial affinities. The negro and Irishman, who are extremely susceptible to tuberculosis, are less so than most races to diabetes. Statistics of the Johns Hopkins Hospital show that the negro, in Baltimore, has only half the susceptibility to diabetes of the general white population. In Ireland the mortality from diabetes is three per 100,000, as compared with seven in 100,000 for England, and five in 100,000 for the whole of Europe. The Jew, who is generally believed to be especially resistant to tuberculosis and in whom the disease certainly often takes a more favorable course than in other nationalities, is singularly prone to diabetes, as are likewise the French and the native populations of India, especially the Hindus. In Paris the mortality from diabetes is fourteen per 100,000. Von Noorden states that at Frankfort the deaths from diabetes among Jews are more than six times the proportion among non-Jews. Bouchardat considers the frequency of diabetes among Hebrews to be due to their fondness for sedentary occupations and disinclination for physical exercise. Von Noorden advances the theory that it is due to a physical degeneracy produced by many centuries of inbreeding. Both tuberculosis and diabetes are more common in cities than in the country, and in both hereditary predisposition is of some account in the ætiology. Fitz and Joslin found heredity to play a role in 23.8 per cent. of their cases of diabetes, Naunyn in seventeen per cent. of the cases reported by him, Bouchardat in twenty-five per cent., and von Noorden in 18.5 per cent. It has even been suggested that under some circumstances diabetes, like tuberculosis, may be communicable, as in the so-called cases of conjugal diabetes reported by Reil and Henke, Oppler, Külz, Schmitz, and others. Naunyn agrees with Senator, however, that these cases are to be explained as coincidences. In both diseases drug treatment is of relatively little value, as compared with the importance of detailed attention to hygiene and diet, and the intelligent coöperation of the patient himself is vitally necessary for any measure of success in either. The prognosis in both is largely dependent upon the social and financial status of the patient, the unfavorable influence of poverty, ignorance, and bad hygienic conditions being most marked. Both diseases exercise a decided effect upon the psychical attitude and morale of the patient. The tendency of the diabetic is to melancholy and a peevish hypochondria. The consumptive, on the other hand, frequently exhibits a blind and fatuous optimism. Finally, both tuberculosis and diabetes are often associated in the same person.

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This association has long been a familiar clinical fact. It was first noted in literature by Richard Morton in 1696, his Latin treatise, entitled *Phthisiologiæ*, containing a chapter *De Tabe a Diabete.* Diabetic phthisis was more fully studied by John Rollo in 1798. Bardsley asserts that all diabetics are attacked with tuberculosis in the latter stages of their disease. Griesinger found tuberculosis to be present in forty-three per cent. of the 250 cases reported by him. Bouchardat found pulmonary tuberculosis nineteen times in nineteen autopsies. Some of the later authorities give a less proportion. Thus Germain Sée states that only twenty-three per cent. of diabetics die tuberculous. Naunyn, in fifty autopsies, found tuberculosis in forty-one per cent. Frerichs found the lungs tuberculous in twenty-five out of fifty autopsies. In most cases the tuberculosis is secondary to the diabetes, but this is not invariably the case. The tissues of the diabetic, which are so vulnerable to eczemas, carbuncles, ulceration of the skin and mucous membranes, furunculosis, and gangrene, show also a peculiar susceptibility to tuberculous infection. Bouchardat believed that the polyuria of diabetes created a predisposition to tuberculosis in much the same way as does the prolonged lactation of milch cows and nursing mothers who bear numerous children in quick succession. The tuberculous tendency of diabetics is now, however, very generally considered to be due to the hyperglycæmia and hyperglycosis of their tissues, for it is well known that the tubercle bacillus has a sweet tooth; Nocard and Roux having demonstrated that it, in common with many other microörganisms, develops most luxuriantly in a culture medium to which sugar has been added.

Before the tubercle bacillus was known diabetic phthisis was often described as a disease *sui generis*, but soon after Koch's discovery Immermann and Rütimeyer demonstrated that the tubercle bacilli are regularly present. There are, however, certain peculiarities in the pathological conditions present in the lungs in tuberculosis accompanying diabetes, which have been well described by Naunyn. The tuberculous, cheesy, infiltration is soft, and there is a tendency to the rapid formation of vomicæ, masses of tuberculous tissue surrounded by a puriform fluid being found in the recent cavities. Some authorities still consider that in diabetes there may be a destructive lesion of the lungs closely simulating tuberculosis without the presence of tubercle bacilli. Such a case has been reported by Roque. Von Noorden is authority for the observation that there frequently exists in the sputum of diabetics a substance which rapidily disintegrates and destroys the tubercle bacillus. Among the curiosities of the literature on the pathology of diabetic tuberculosis is a case reported by Schindelka of a diabetic dog with a complicating tuberculosis of the lungs. Examples of a similar association have been observed in apes.

In view of the emphasis which has been attached in recent years to the pancreatic origin of diabetes it might be surmised, perhaps, that in the exceptional cases in which tuberculosis precedes the development of diabetes there might be found a tuberculous lesion of the pancreas as a cause of the latter disease. Such, however, is not the case. Kudrewetski found in a series of 128 cases of tuberculosis of the lungs the pancreas was affected but fifteen times, and in these cases diabetes is not noted as having been present during life. Primary tuberculosis of the pancreas, if it exists at all, is certainly extremely rare. Delafield and Prudden do not mention it as occurring. Cornet says that tuberculosis of the pancreas is always secondary. The only cases referred to in literature are two cited by Senn, one of which was reported by Wilson in 1829, the other by Aran in 1846. Both of these cases antedated a time when any very exact or certain determination of the tuberculous nature of the lesions was possible and in neither case was diabetes present. The usual lesions of the pancreas in diabetes are an interstitial pancreatitis, atrophy of the gland, a diffuse arteriosclerosis, or a hyaline degeneration of the cells of the islands of Langerhans. Tuberculosis, as a cause of diabetes, may then be dismissed.

Frequent as is the association of the two diseases, one or the other in its early stages is not infrequently overlooked. It is a safe rule in practice to make repeated examinations of the chest in diabetics, and in tuberculosis the urine should be periodically examined for glucose. Tuberculosis of the lungs in diabetics, especially of the obese type, frequently runs an atypical course. There is often observed a somewhat characteristic, reddish cyanosis of the face instead of the ordinary pallor or hectic flush of tuberculosis. The cough is often slight and attended by little or no expectoration. Sugar may sometimes be demonstrated in the sputum, and the pulmonary lesion may terminate in gangrene, which is not attended by the characteristic fœtor of ordinary gangrene of the lungs. The appetite is usually well preserved and may even be greater than in health. The temperature may not be elevated, and night sweats are often not present. Seegen and von Leyden state that hemorrhages are of rare occurrence on account of the higher specific gravity and greater viscosity of the blood. Dieulafoy, however, does not consider hemorrhages infrequent in diabetic comsumptives. On the other hand, if the tuberculosis is the prominent feature, the diabetes may escape recognition. It has been frequently observed where phthisis develops in a subject of diabetes there may be a marked diminution in the quantity of urine and the percentage of sugar will fall. These changes, however, are delusive signs of improvement. The diabetes continues unchecked, and is hastened in its progress by the complicating tuberculosis. In the later stages the dry, itching skin of the diabetic becomes moist and there may be profuse night sweats.

Gouty diabetics are said to seldom develop tuberculosis. Rénon has reported at least one such case, however, and others have been described by Charcot, Brouardel, and Naunyn. Diabetics who neglect their diet and thus invite an access of glycosuria are more likely to become tuberculous than careful, conscientious patients who observe a strict regimen.

The recognition of the coexistence of diabetes and tuberculosis has an important bearing upon the prognosis and treatment of the patient. Not infrequently in examining tuberculous patients, cases are discovered to be diabetic who have had no instruction as to diet and who have been receiving a syrupy cough mixture and cod liver oil with extract of malt, the latter consisting of more than fifty per cent. maltose, which is immediately converted into grape sugar in the intestine. Some of these patients are found also to have a marked acidosis, evidenced by the presence of acetone, diacetic acid and beta oxybutyric acid, with an excess of ammonia in the urine. The presence of these acetone bodies, which are to be regarded as a forerunner of the danger of coma, makes it a question of more than theoretical interest whether the administration of large quantities of oils and fats, which is an important part of the dietetic treatment of tuberculosis, may not possibly in some cases hasten a fatal termination in diabetic coma. Magnus Levy has shown that beta oxybutyric acid is in part, at least, derived from fats, and this is the parent substance of the other acetone bodies, diacetic acid and acetone, into which it is readily changed. In this connection the experimental evidence of Grube is interesting, that pork fat is peculiar in not being a source of beta oxybutyric acid. It would seem practical wisdom in cases showing strong reactions, with the ferric chloride and sodium nitroprusside tests, with high dextrose percentage in the urine, to limit the quantity of butter, cream, and oils—with the possible exception of pork fat—and substitute for such tuberculous diabetics alcohol, which Atwater and Benedict have shown may take the place of fats and carbohydrates as a source of energy, and thus spare, in a measure, the excessive tissue waste which is a conspicuous symptom of both diabetes and tuberculosis. The combustion equivalent of alcohol is seven calories, of fat 9.3 calories, and of sugar four calories. Another indication for the administration of alcohol in diabetes is the presence of acetone substances in the urine. Langstein and von Noorden agree that the effect of alcohol is to diminish acetonuria, and patients taking alcohol in moderate amount show no increase in the sugar content of the urine. The quantity should not exceed two ounces daily, in the form of pure whisky, gin, cognac, or a dry wine. A rational therapy in the acidosis of diabetes also demands an additional allowance of carbohydrate food and the exhibition of alkalies to overcome the diminished alkalinity of the blood. An excessive flesh diet is also considered to be favorable to the acid intoxication which is believed to be a factor in producing diabetic coma. The difficulties in the prevention and treatment of this grave condition are thus apparent.

These difficulties are not diminished by the fact that von Noorden and others are now inclined to doubt the entire theory of acidosis as promulgated by Stadelmann and Naunyn. For those who believe that the acid toxæmia of the acetone substances is adequate to account for the phenomena of diabetic coma, theoretically, all classes of food are more or less contraindicated, carbohydrates on account of their failure to be oxidized and their excretion as sugar, fats on account of their splitting up into fatty acids, and proteids because in excess they also produce acidosis. The only escape from this blind alley is to treat the patient without too much regard for theory. No abstract considerations should determine the diet. The patient's tolerance for carbohydrates must, in every case, be carefully established, and as liberal and varied a diet permitted as is possible. It is better for the patient to gain weight and improve in health with an increased percentage of sugar than to lose ground with a reduction in the glucose content of the urine. The case is even more difficult with a complicating tuberculosis present. Some authorities advise ignoring the diabetes and treating only the tuberculosis. Dieulafoy in these cases excludes only sugar from the diet. Naunyn has shown, however, that great benefit may be derived by the tuberculous patient with diabetes from a carefully regulated diet. Fortunately many of the indications for treatment are the same for both diseases. A diet of meat, fat, cheese, and eggs is equally good for both. Milk may often be permitted for diabetics, especially when sour or artificially fermented. The drug of greatest value in diabetes, opium, with its derivatives, codeine and heroin, is also indicated for the cough, the hemorrhages, the diarrhœas, and to promote the euphoria of the advanced consumptive. The diabetic consumptive is very often afebrile, and for such cases exercise in moderation in the fresh air is not contraindicated. Such exercise is distinctly useful for the diabetic, as it has been shown that larger quantities of carbohydrates are tolerated on account of the increased consumption of sugar by the muscles during exercise. Creosote and guaiacol carbonate, which have continued in favor for tuberculosis, are also believed to relieve the symptoms of diabetes, notably the thirst and polyuria. Arsenic and strychnine, which have their advocates in diabetes, are good systemic tonics for the consumptive. Hydrotherapeutics are valuable in both diseases, as are also the alkaline mineral waters, woolen clothing next the skin, abstinence from tobacco, freedom from worry and care, and a quite life in the country in a mild, dry, and equable climate.

The prognosis in either disease is sufficiently grave. A diabetic, however, after the age of fifty, with careful dietetic management, may prolong his life for many years and maintain a fair condition of health. Tuberculosis also, developing after middle age, often assumes a relatively benign and non-progressive character. The lesions in the lungs are frequently of a fibroid type, tending to spontaneous arrest. Such a consumptive, with suitable hygiene, diet, and careful regulation of his life, may live out all his days and die of some unrelated disease. But usually when diabetes and tuberculosis are associated in the same individual, the mortality is so high as to make treatment of little avail. Naunyn, however, has reported the case of a diabetic, aged fifty-three, who was attacked with tuberculosis in both lungs and tuberculous ulceration of the larynx, in whom the pulmonary process was arrested, the ulcer of the vocal cord healed, and the patient was in good health sixteen years later. Fraenkel has reported a case of apparent cure in a diabetic physician with well marked tuberculosis of the lungs. Such cases, unfortunately, must be regarded as extremely rare. A practical conclusion which cannot be too strongly urged is the importance of safeguarding the diabetic from tuberculous infection. Diabetics should be rigorously isolated from members of their family who are tuberculous. A recent case at the tuberculosis clinic of the Presbyterian Hospital well illustrates the danger of household infection. A young Irishman, who has been a diabetic for a year and a half, has lived in a tenement with his married sister, who has for three years been a consumptive of rather careless habits. Five months ago he began to cough and has now a well marked lesion of the right upper lobe. A similar case is related by Rénon. A man of sixty, who had been a diabetic for many years, but whose general condition was excellent, had a daughter aged twenty-one who became tuberculous. The father was intimately associated with her while she was taking climatic treatment in the south of France. The daughter died in a few months of acute phthisis. The father also was attacked with tuberculosis of the lungs of a rapidly progressive type, and died several months after the death of his daughter. Obviously, diabetics should not be received in hospital wards which harbor consumptives, nor should they frequent health resorts which are visited by large numbers of tuberculous patients.

Of six cases of associated diabetes and tuberculosis recently under observation at the tuberculosis clinic of the Presbyterian Hospital, in all but one the diabetes preceded the development of the pulmonary disease. In this case the patient was undoubtedly tuberculous at least a year and a half before the appearance of any diabetic symptoms. Her diabetes developed during pregnancy and she was delivered of a seven months' child which lived eight weeks. In four cases the tuberculosis developed eighteen months, twelve months, seven months, and two months, respectively, after the patients were known to be diabetic; in the remaining case the time could not be ascertained. This patient, a Hungarian Jewess, died seven months after the development of her tuberculosis. Three of the six patients were Hebrews. In four of the patients the family history was negative, both as to diabetes and tuberculosis, in one case a maternal aunt had diabetes, and in one, as already noted, the patient was probably infected with tuberculosis by a consumptive sister. Four of the cases were afebrile, and in the other two the temperature at no time has been above 100° F. The cases were equally divided as to sex. In the three women pruritus vulvæ was a marked symptom. In four out of the six frequent and considerable hæmoptyses were present. Tubercle bacilli were found in the sputum of three and were absent in three patients. In one patient it was possible to demonstrate the presence of glucose in the sputum with the phenylhydrazin test. The urine showed a strong reaction for acetone in all patients, and in one diacetic acid was also present. A trace of albumin was found in four of the six urines examined. The largest total quantity passed in twenty-four hours was seven and a half quarts, the highest specific gravity was 1.047, the greatest percentage of glucose noted was 7.2, estimated by the polariscope. In one case glucose was present in a urine of very low specific gravity, 1.009. The appetite was excessive in one patient, good in two, variable in two, and poor in one. Of five patients in whom the patellar reflexes were tested, they were abolished in but one. Bouchardat first directed attention to the fact that in diabetes the knee jerk is frequently absent. In one case a complicating laryngeal tuberculosis was present. In the case showing the highest specific gravity and greatest sugar content of the urine the patient several times appeared to be threatened with coma, as evidenced by great muscular prostration, irritability, sighing dyspnœa, drowsiness, and syncopal attacks. The husband of this patient has recently been attacked with tuberculosis of the lungs—apparently a clear case of conjugal infection. In a case of combined tuberculosis of the lungs and diabetes in a Cuban at St. Joseph's Hospital there was an extreme degree of ichthyosis of the skin of the entire trunk and limbs. In this case, as in a similar one reported by Lebert, the ichthyosis had existed for many years prior to the diabetes and tuberculosis.

The majority of the cases of this association of tuberculosis of the lungs with diabetes which I have seen have been in dispensary practice, and it is felt that, as a rule, in such practice insufficient care is taken in supervising the details of treatment of the diabetic element. In recent years, through the installation of nurses and better equipment of the outdoor departments of hospitals, there has been great improvement in the dispensary care of tuberculous patients, but the diabetic is still comparatively neglected. His diet should be at least as carefully prescribed as his medicines, and the ready-made printed diet sheet does not meet this indication. A valuable and seemingly practicable extension of the work of district nurses and the diet kitchen, which has been so helpful in the tuberculosis clinic, would be instruction in the preparation and supervision of food for the diabetic, which is now very imperfectly attended to in the tenement home. This comparative neglect of diet is a difficulty which is also experienced in the care of the well-to-do diabetic. It is not possible in this country to send diabetics to well managed institutions where there are the modern facilities for dietetic treatment under expert supervision which exist abroad. It is probable that the patient who does well at Neuenahr, Carslbad, or Vichy is as much indebted for his improvement to the painstaking attention to dietetic detail of the local physicians, and to the intelligent coöperation of the hotels and pensions in providing an attractive, ample, and varied menu which makes the dietetic cure a pleasure, as to the alkaline mineral waters which are drunk so seriously in these places. To Külz is due the credit for having first emphasized the importance of institutional treatment for the diabetic. In both tuberculosis and diabetes the careful regulation of the patient's daily life is the important factor, and this can, in most cases, probably be most easily and most efficiently carried out in a well conducted sanatorium. When the two diseases coexist the care of such a case is a dispiriting and usually fruitless task for the physician, but the unfortunate patient's condition may, at least, be made more tolerable, his life may be prolonged, and in rare cases he may, perhaps, recover through wisely directed and faithfully continued adherence to the necessary hygienic and dietetic requirements.

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XV.

A MALIGNANT ADENOMA OF THE ADRENAL WITH TRANSFORMATION INTO SARCOMATOUS TISSUE.

By J. C. Meakins, M.D., Resident Pathologist.

Malignant adenomata of the adrenal are uncommon, and especially uncommon are adenomata which show in the primary tumor or in the metastasis sarcomatous transformation. Such a condition is paradoxical, but the embryology of the adrenal affords an explanation. It was formerly believed that the cortex of the adrenal develops from the mesoblast and the medulla from the epiblast. The studies of Janosik and Gottschau, Minot[1] and Aichel,[2] have established the fact that the entire adrenal develops primarily from the mesoderm. The mesoderm divides into two parts: the mesochymal part forms the connective tissues, and from the mesothelial part develop the serous membranes, the genito-urinary tract (except the urinary bladder) and the striated muscles. The mesothelial structures undergo greater differentiation than mesochymal tissues and take on certain "epithelial" characters.

It may be assumed that the cells of a malignant tumor do not acquire new features but revert to a former state; there is reversion first to the characters latest acquired and finally to the original embryological condition. This view may help to explain peculiarities of the following case. Since the cells of the adrenal are mesothelial in origin and assume epithelial functions, tumors arising from them may exhibit epithelial characters of new growth, but revert to the primitive mesodermal type more readily than cells primarily of epithelial origin.

The patient with the tumor, which will be described, was admitted to the Presbyterian Hospital on January 6, 1908, in the service of Dr. Eliot. I wish to express my thanks to Dr. Eliot for permission to report the following facts concerning the history of the case:

The patient, W. N., was white, male, aged forty-five years, and by occupation a letter carrier. His family history is unimportant. He was born in the United States, where he has always lived. Many years ago he used alcohol in moderation; he had gonorrhœa in 1897. Otherwise his history contains nothing noteworthy.

In 1905 the patient had hematuria for a week without subjective symptoms. He remained in good health until December 24, 1908, when he noticed that his urine was dark brown. Three days later he suddenly developed severe pain in the left flank. It was not influenced by deep respiration or by movement, but on assuming the right lateral position it was greatly increased. No bright red blood was observed in the urine.

Physical examination revealed a prominence in the left flank and on palpation a large, tender tumor was found in this region. It disappeared under the costal margin and could be moved only in an antero-posterior direction. There was flatness from the fourth intercostal space to the crest of the ileum, concealing the splenic dullness. When the patient assumed the right lateral position the tumor approached almost to the median line. The heart, lungs and nervous systems were normal. Blood examination showed no abnormality.

The urine was dark brown, acid, and had a specific gravity of 1020. It contained about 0.1 per cent. albumin, and no glucose. Microscopical examination revealed hyaline and granular casts, many red blood cells, leucocytes and epithelium. Urea was 2.7 per cent. The ureters were catheterized and the urine from the two sides had practically the same characters, but the right kidney was excreting the greater amount.

On January 6, 1908, Dr. Eliot found at operation a large, firm, nodular mass, occupying the site of the left kidney. It

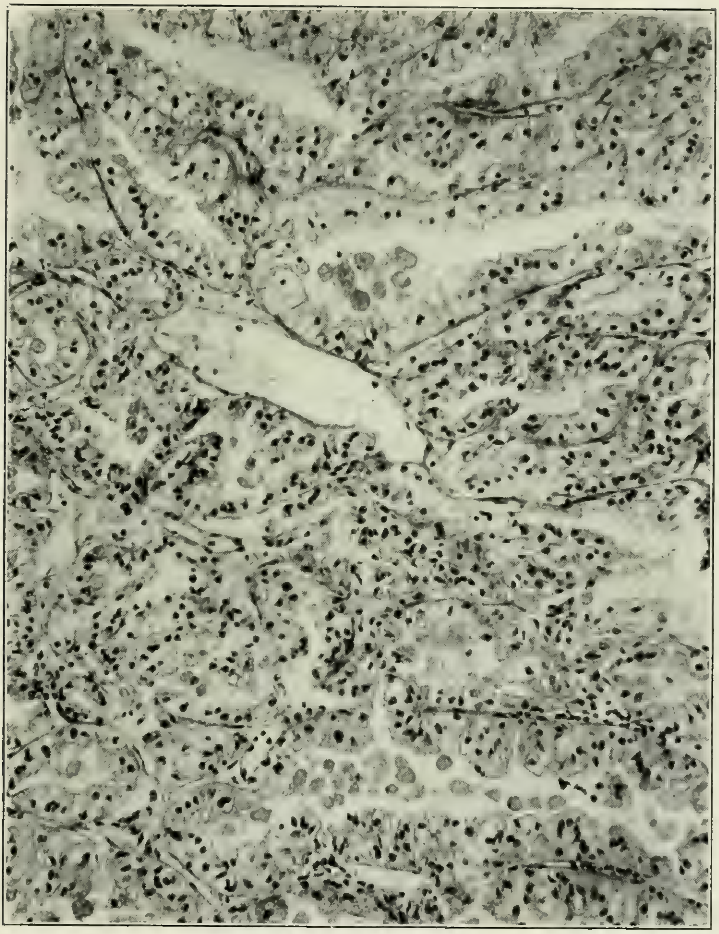

FIG. 1—ADENOMATOUS TISSUE

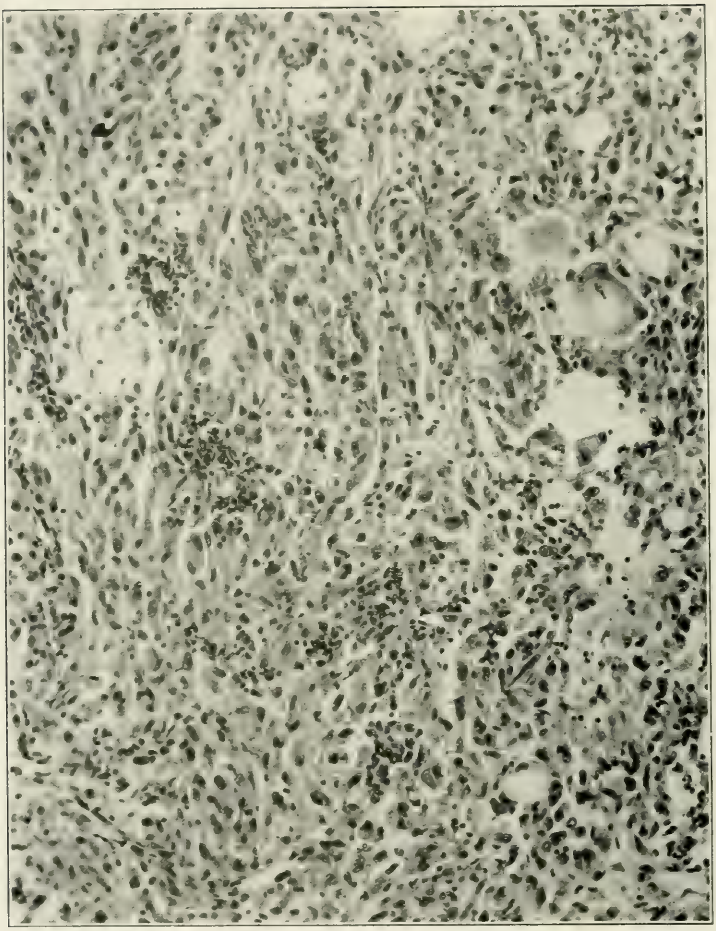

FIG. 2—SARCOMATOUS TISSUE

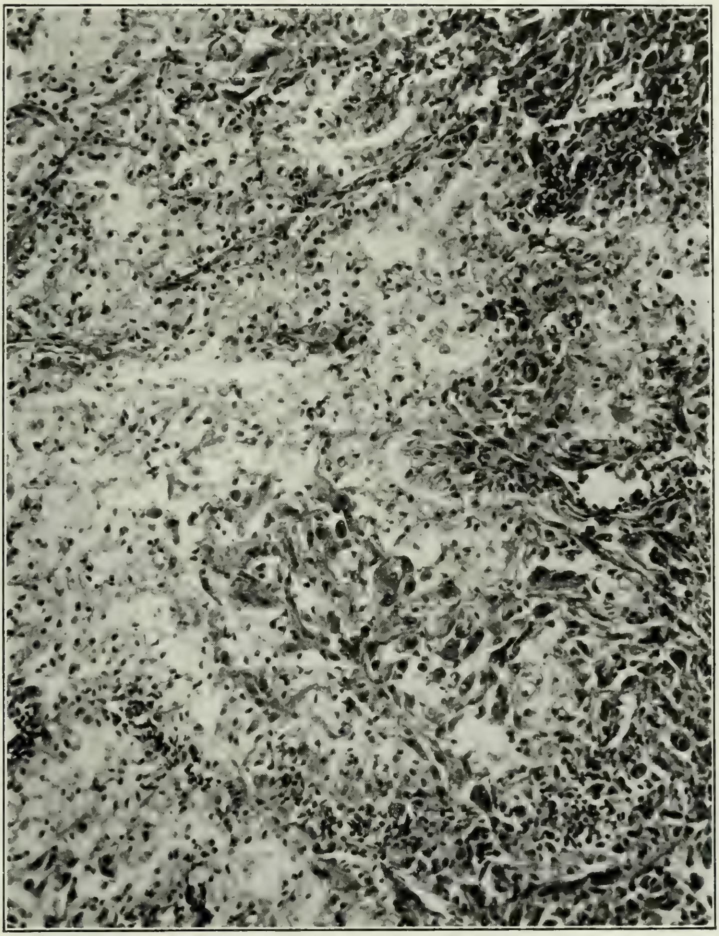

FIG. 3—TRANSFORMATION FROM ADENOMATOUS INTO SARCOMATOUS TISSUE

extended from above the costal margin downward almost to the crest of the ileum. The tumor pushed the peritoneum forward and to the right, but was completely retroperitoneal. It was removed with great difficulty and there was considerable hemorrhage.

PATHOLOGICAL EXAMINATION.

The specimen has the general shape of a kidney, measuring 18x11x10 cm. The outer part consists of a thick layer of perirenal fat in which are imbedded tumor nodules of various sizes. These tumors are yellowish white and very friable. They contain many blood-vessels and into some of the nodules hemorrhage has occurred. Many of the larger masses seem to infiltrate the surrounding fat. This perirenal mass, although thickest at the upper pole, completely surrounds the kidney and is removed with little damage to the kidney substance.

The kidney measures 13 x 7 x 4 cm. The posterior surface is smooth and the anterior surface and the borders contain tumor nodules similar in character to those in the perirenal fat. After longitudinal section through the pelvis the kidney is found almost entirely replaced by new growth. The only part of the cortex which remains intact is upon the posterior surface of the organ. The tumor nodules may be divided into two varieties, according to the color and consistence. The nodules of one variety are white, more or less granular and very friable. Those of the other variety are yellowish and firm. In some nodules the two varieties are combined and merge into each other. The white nodules exhibit a tendency to infiltrate the surrounding structures. Reference will be made later to this distinction.

Microscopical sections were made through different parts of the new growth and the changes which were found may be divided into two groups. In some sections the cells had the typical appearance and arrangement of adenoma, while in others the arrangement was sarcomatous.

Adenomatous Tissue.—The histological appearance presented by the tumor tissue of this type is entirely different from that observed in the sarcomatous areas. The difference is not so much in the character as in the shape and arrangement of the cells. The cells are cuboidal with a faintly staining protoplasm which is finely granular. The nucleus is usually situated near the periphery of the cell. It is round and vesicular, with a deeply stained nucleolus and a pale chromatin network. These cells closely resemble those of the adrenal cortex.

The cells in a single layer are arranged to form tubular alveoli. The alveoli are usually straight, but occasionally are tortuous. The lumina are patent and frequently contain débris derived from desquamated cells. Between the alveoli there are fibrous trabeculæ fairly rich in cells. The reticulum is well demonstrated by Van Gieson's stain, and does not extend between the tumor cells. Broad bands of connective tissue separate the tumor into lobules, and from these bands the trabeculæ between the alveoli are derived. (Plate I).

In some of the larger tumor masses of this type the cells at the periphery of the mass differ from those in the centre. In the centre the cells tend to lose their distinctly alveolar arrangement. The lumen disappears and the trabeculæ become less distinct. The cells at the same time become longer, although the nucleus does not change.

Sarcomatous Tissue.—There are found in such parts of the tumor various types of cells which may be grouped in three classes. (1) Some of the cells closely resemble those of the normal adrenal cortex. They have a large, deeply staining nucleus, which, as a rule, is round, but occasionally assumes an oval shape. The cell body is small and, corresponding in shape to the nucleus, is round or oval. The protoplasm takes eosin poorly. These cells are not numerous or uniformly distributed but occur in small collections, chiefly about the blood-vessels. Under the low power of the microscope they closely resemble lymphocytes but, with a high magnification, a difference is apparent. (2) Closely associated with these cells there are large spindle-shaped cells which form the greater part of the tumors. The protoplasm of these cells stains poorly and contains fine granulations and sometimes small vacuoles. The nucleus is large and as a rule spindle-shaped, but frequently is irregular in shape. It stains poorly and has a fine chromatin network; there is a deeply staining nucleolus which is situated towards one end of the nucleus. (3) Besides these cells there is a large irregular cell with a faintly staining irregular nucleus. The cell body contains many vacuoles, some of which are large and appear to fill the whole protoplasm, displacing the nucleolus. (Plate II).

A series of transitions between the three kinds of cells described above indicates that they are all derived from the same source, namely, the cortical cells of the adrenal. Mitotic figures are very common, and both regular and irregular types are observed. Multinucleated cells are frequently found and the nuclei are usually arranged at the periphery of the cell.

In sections stained with Van Gieson's stain broad bands of connective tissue are found, separating the tumors into lobules. In addition a few fine strands of reticulum are occasionally found between the cells, but as a rule the cells are closely packed together. This is especially true where the spindle cells predominate. These cells are arranged with their long diameters more or less parallel, but without any evidence of alveolar arrangement.

The blood-vessels are abundant and are in intimate contact with the tumor cells. In fact the walls of the veins in many places are formed by tumor cells covered by endothelium, and occasionally a vein was found whose lumen the tumor had invaded. A section through the vessels at the hilus of the kidney shows one of the smaller veins almost completely obliterated by a parietal thrombus. A mass of tumor cells found at the point of attachment of the thrombus appears to be the cause of the thrombosis.

The sarcomatous type of tissue is present alone in the white, friable nodules, described above, and is the predominating form of tissue in the perirenal mass; these tumor nodules invade the surrounding tissues. In the kidney substance the nodules of this type are large and ill defined, showing invasive characters. The yellowish nodules have the histological structure of adenoma and are circumscribed. In some of the tumor masses both white and yellow tissue is found, and in these nodules sarcomatous and adenomatous structures are side by side. As a rule, the two types are well isolated by bands of fibrous tissue, but in some places the adenomatous structures exhibit the loss of alveolar arrangement described above; the cells become spindle-shaped and their nuclei take on an oval form and become paler. A complete transition may be traced in the same tumor from a purely adenomatous structure to one with typical sarcomatous cytology and arrangement. (Plate III).

In accordance with the embryology of the adrenal, all malignant tumors of the gland should be classed as sarcomata, but from the histology of the normal gland carcinomata might be expected to develop. In the present case the larger masses exhibit the cellular characters of sarcoma. There is, however, evidence to show that these tumors may have had originally a carcinomatous structure, and as the growth progressed the reversion to the mesothelial or sarcomatous type of cells occurred. In fact such transformation or reversion is demonstrated in some of the tumor masses. If these tumors had had opportunity to continue their growth, reversion to sarcomata would, perhaps, have become complete.

Jores[3] has described a sarcoma of the adrenal in which a direct transition could be traced from the normal adrenal cells to the cells of the sarcoma. In this case metastases in the brain were of the same structure as the main tumor. In another case he describes an alveolar sarcoma of the adrenal which in places resembles slightly the histological structure of carcinoma. On the evidence afforded by these cases Jores believes that all malignant tumors of the adrenal are sarcomata, although they may resemble in some parts carcinomata.

Rolleston and Marks,[4] after a careful study of tumors of the adrenal, make the following statement: "Our own impression is that malignant tumors of the suprarenal bodies are peculiar and form a special class. They may approach structurally either the carcinomata or sarcomata, and sometimes one and the same tumor may in different parts resemble both."

Woolley[5] has reported a case in which a transition was demonstrable between the adrenal cells and a primary adenoma of the adrenal, accompanied by metastases, all of which were sarcomatous. He believes this condition is explained by the embryology of the adrenal, and thinks that such malignant tumors should be called "mesothelioma."

Such cases show that tumors of the adrenal may begin as sarcoma or as carcinoma and revert to a sarcomatous type of tissue. Such reversion may occur as a direct transformation from the normal adrenal cells to sarcomatous or carcinomatous cells, or may occur in metastases from the original adenoma; or, as in my own case, may be followed by a series of transitions within the same tumor nodule.

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XVI.

A CASE OF GANGRENE OF THE OMENTUM DUE TO TORSION.

By George Woolsey, M.D.

Torsion of the omentum is of such uncommon occurrence that the following case seems worthy of record:

Mr. A. A., twenty-three years of age; Russian; single; druggist; was admitted to the Presbyterian Hospital July 26, 1908 (Hosp. No. 6353). Family history negative. Previous history: seven years ago he was ruptured playing football. In May, 1906, he had pain in the hernia, but this soon disappeared. In March, 1907, it became irreducible and painful, and he was operated upon. The patient says that the wound was allowed to granulate up from below. Present history: Saturday afternoon, July 23, he was suddenly seized with severe pain across the lower part of the abdomen which he attributed to pears eaten the day before. As the bowels had not moved that day or the previous one he took magnesium citrate, and then other cathartics, without relief. The pain became a dull continuous ache and extended into the right inguinal region, so that he thought the old hernia had reappeared. That night he felt prostrated, and weak in the lower limbs. On going to bed he noticed a swelling the size of a small egg in the right inguinal region, which did not disappear on lying down. The pain continued, but did not increase, in the lower abdomen and the right inguinal region, and there was sharp pain here on deep inspiration. There was no passage of gas or stool. Hot and cold local applications gave no relief. There was no vomiting. Micturition was normal.

On examination the abdomen is symmetrical, but moves less freely on the right than on the left side in respiration. There is marked rigidity in the right lower quadrant, with dullness extending into the right flank. There is tenderness over the whole lower abdomen, more marked on the right side. No distinct mass is felt. In the right inguinal region, at the site of the old hernia wound, there is considerable puffiness. The right testicle is absent. Temperature 102.5° F., pulse 96, respiration 22.

The diagnosis of a probable appendicitis with intestinal obstruction was made, and operation was performed under gas and ether anæsthesia, July 26th. Under anæsthesia a rather firm mass was found in the right iliac fossa and the hypogastrium, extending about 1.5 inches to the left of the median line. Percussion over this was dull, and it did not feel like an ordinary appendical abscess. However, an incision was first made over the appendix, which was found normal. There was a darkish sero-hemorrhagic fluid in the peritoneal cavity, and extending toward the median line from the incision was a dark mass. Through a median incision this was made out to consist of gangrenous omentum of the size of a small grape fruit. When this mass was displaced to the left the undescended right testis, fully developed, appeared in the wound, having a long mesorchium. The internal abdominal ring was explored and found open. There was no gut or omentum in it, though a small tongue of omentum, appearing gangrenous, may have been in it. There was a large amount of sero-hemorrhagic fluid, with no odor. The mass extended almost up to the umbilicus and was somewhat adherent to the surrounding intestines, though the adhesions were easily separated. Above the mass the omentum was twisted from right to left into a rope-like band, which required three and one-half twists in the opposite direction to undo. The omentum was ligated in healthy tissue about two inches below the transverse colon and the mass was excised. The rest of the abdominal cavity appeared normal. Both wounds were closed without drainage.

The patient made an uneventful recovery. At first he complained of considerable abdominal pain and distension, which were relieved by enemata. There were some fecal results from these enemata, and on the third day he had two movements from catharsis. The wounds healed by primary union. Blood counts, July 26, leucocytes 9,100, polymorphonuclears 85 per cent.; July 30, leucocytes 5,300, polymorphonuclears 68.5 per cent.

The etiology of this condition is not thoroughly understood, but most of the reported cases have been associated with hernia, and it is thought that the traction of the omentum in the hernial sac pulls out its upper part into somewhat of a band which can become more readily twisted than the normal broad omentum. If the lower part of the omentum, in the hernial sac, forms more or less of a conglomerate, as is often the case, it may be more readily rotated by the movements of the intestines or by some external force, than the normal omentum. If the omentum is adherent in a hernial sac there must be a twist both above and below the gangrenous part. In some reported cases there has been no previous hernia. In the case here reported the hernia had been operated upon and there was no hernia at the time. How many twists are required to produce gangrene, and whether the omentum is often twisted slightly but not enough to cause gangrene, we do not know. In the case reported the small mass in the inguinal region, felt by the patient, was doubtless the undescended testis and not the gangrenous mass of omentum. In symptomatology this case conforms to the rule with the presence of obstinate obstipation without vomiting, and like most cases it was operated on for appendicitis or obstruction of the bowels, though that diagnosis seemed very doubtful after the examination under anæsthesia.

XVII.

THE VALUE OF THE LEUCOCYTE COUNT AND THE DIFFERENTIAL BLOOD COUNTS IN APPENDICITIS.

By G. N. Pease, M.D., Second Assistant House Physician.

A good many papers have appeared recently in regard to the value of the blood count in appendicitis. So far we do not seem to have reached any definite conclusions as to what part of the blood count will enable us to judge most accurately of the pathological lesion present. To add to the data already published and to see how the cases in this Hospital compare with those already presented, is the purpose of this paper.

The following series of 300 cases is taken from the services of Drs. McCosh and Eliot in this Hospital. They are the last 300 cases operated on in this Hospital. All the cases presented went to operation, and in each case a definite determination of the pathological lesion was possible. In almost all of the cases the blood counts were taken on the day of the operation or the day before the operation, and no count dates back more than twenty-four hours previous to the operation.

The leucocyte counts in each case were made by the Junior Surgical Interne in the Hospital. The differential counts, on the other hand, were practically all made by the Pathological Externe and were, therefore, all counted by the same individual, which in a series of cases like the present should make a very reliable comparison of the different cases.

The following classification was adopted as best grouping and indicating the pathological lesions present:

1. Chronic Appendicitis—including acute cases that have subsided and all interval cases.

2. Simple Acute Appendicitis—cases presenting signs and symptoms of an acute process localized to the appendix itself, but without gangrene.

3. Acute Gangrenous Appendicitis—simply a further development of acute appendicitis.

4. Appendicitis with Abscess Formation—cases with pus walled off about the appendix.

5. Appendicitis with local peritonitis or peritonitis spreading to neighboring regions, such as the pelvis, but not yet general.

6. Appendicitis with general peritonitis.

TABLE NO. I.

This shows the number of cases of each variety of appendicitis in this series and the average number of leucocytes and polymorphonuclear cells present in each class of cases.

Variety.	No. of Cases.	Average No. of polymorph. Leucocytes.	Average number of Leucocytes.
Chronic	63	69%	12,900
Simple Acute	47	77	14,700
Gangrenous	28	85	19,400
With Abscess	14	88	22,200
With Local and Spreading Peritonitis	101	88	21,100
General Peritonitis	47	89	21,800

The above table shows, as we have already learned to expect, that the more severe the pathological lesion the higher is the leucocyte count and the higher the percentage of polymorphonuclear cells in the differential count. An apparent exception to this is the leucocyte count in appendicitis with localized abscess, as compared with the count in cases with general peritonitis. In case of abscess, the average leucocyte count was a little higher than in general peritonitis, yet we classify general peritonitis as a much more severe lesion. The explanation of this probably lies in the fact that in many cases of general peritonitis the infection was so virulent that it completely overwhelmed the bodily resistance and there was no reaction to the invasion. For example, a good many of the cases of general peritonitis gave counts like the following:

Leucocytes, 5,000. Polynuclear, 71 per cent.
Leucocytes, 8,000. Polynuclear, 68 per cent.
Leucocytes, 7,500. Polynuclear, 79 per cent.

Such counts would, of course, greatly reduce the general average leucocyte and polymorphonuclear counts in the cases of general peritonitis.

Table No. II.

This shows the leucocyte counts in the individual cases of the six varieties of appendicitis mentioned above.

Variety.	Under 10,000	10,000 to 15,000	15,000 to 20,000	20,000 to 25,000	25,000 to 30,000	Over 30,000	Total cases.
Chronic	20	23	16	1	3	0	63
Simple Acute	11	15	11	7	1	1	47
Gangrenous	2	6	10	6	3	1	28
With Abscess	1	3	2	4	2	2	14
With Local and Spreading Peritonitis	5	16	29	29	9	13	101
With General Peritonitis	4	11	10	8	3	11	47

From the above table we see that it is impossible to decide upon the pathological lesion present from the leucocyte count alone. For example, we find 20 out of 63 cases of chronic appendicitis with leucocyte counts of over 15,000, and 21 out of 101 cases of localized or spreading peritonitis, and 15 out of 47 cases of general peritonitis, with leucocyte counts under 15,000. The latter two varieties, of course, being much more severe lesions, should, if the rule were absolute, have leucocyte counts far above 15,000. Practically all that can be said from the leucocyte counts alone is that the majority of cases with leucocyte counts of over 15,000 are severe cases and the majority of cases under 15,000 are mild cases, but there are many cases of both types that do not conform to this rule.

Table No. III.

This shows the percentage of polymorphonuclear cells in the individual cases of the different varieties of appendicitis.

Variety.	Under 75%	75–80	80–95	85–90	90–95	Over 95	Total cases.
Chronic........................	41	11	8	2	1	0	63
Simple Acute....................	17	9	7	11	3	0	47
Gangrenous......................	5	0	6	11	5	1	28
With Abscess....................	0	1	4	5	2	2	14
With Local and Spreading Peritonitis	4	10	16	27	36	8	101
With General Peritonitis..........	4	4	4	19	13	3	47

On examining table No. III we find that we can judge much more accurately of the pathological lesion present from the polymorphonuclear count than from the leucocyte count. We see that practically two-thirds of all the more severe cases show a polymorphonuclear count of over eighty-five per cent. By the more severe cases we mean the last four varieties in the table, namely, (1) acute gangrenous appendicitis, (2) appendicitis with abscess, (3) appendicitis with localized or spreading peritonitis, and (4) appendicitis with general peritonitis. And we see that cases with a polymorphonuclear count of over ninety per cent. are mostly cases with peritonitis either localized, spreading, or general.

Cases with a polymorphonuclear count below eighty per cent. are, as a rule, cases of chronic and simple acute appendicitis. A few cases with peritonitis come below eighty per cent. and these are the exceptional cases mentioned above. Between eighty and eighty-five per cent. we find a number of cases of all varieties, and it only seems possible to designate cases in this column as "doubtful."

Our conclusions then, from Table III, would be:

1. A polymorphonuclear count between eighty-five and ninety per cent. indicates the presence of a severe process.
2. Above ninety per cent., a dangerous condition, probably complicated by peritonitis.
3. Below eighty per cent., safety, for the time being.
4. Between eighty and eighty-five per cent., doubtful.
5. These rules hold good for about four-fifths of this series of cases, there being many exceptions to each rule.

It is not the object of this paper to form any definite rule by which we can tell from the blood count when to operate and when not to operate in a given case of appendicitis. In fact, one point, and probably the most important that this investigation has taught the writer, is that it is impossible to decide from the blood count what pathological condition we shall find, or even determine whether the case is severe or not. There are many exceptions, and these we must learn to recognize by other means at our command.

One of the most recent methods, and one which has aroused more investigation along the line of the value and interpretation of the blood count in appendicitis, is that suggested by Dr. C. L. Gibson of New York City.* He advanced the idea that the relation between the total leucocyte count and the percentage of polymorphonuclears gave the most valuable information; 10,000 leucocytes with seventy-five per cent. of polymorphonuclears was taken as a base line representing the normal relation. With every rise of 1,000 leucocytes there should be a corresponding rise of one per cent. of polymorphonuclears to maintain the normal relationship. Lines were drawn from the leucocyte count to the polymorphonuclear count and designated as horizontal, rising or falling lines, according to the relationship between the leucocyte and the polymorphonuclear count. In brief he says: "If the line connecting the levels of the leucocyte count and the polymorphonuclear count runs pretty nearly horizontal, whether up or down, with only 2-4 points of difference, it indicates that a lesion, whether severe or not, is well borne and therefore of good prognosis. If the difference of level between the two points is considerable, say ten or more units, we are quite sure to have a pretty severe lesion."

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* Annals of Surgery, April, 1906. "The Value of the Differential Leucocyte Count in Acute Surgical Diseases."

The following table (Table IV) gives the result of applying Dr. Gibson's method to our series of cases:

TABLE NO. IV.

Variety.	Rising Line.	Falling Line.	Horizontal Line.	Rising Line. 5 units or more.	Total cases.*
Chronic	13	41	9	3	63
Simple Acute	24	15	8	9	47
Gangrenous	14	10	4	7	28
With Abscess	9	5	0	5	14
With Local or Spreading Peritonitis	58	37	6	36	101
With General Peritonitis	23	23	1	19	47

* To explain the totals it must be remembered that the cases in column four—namely, those showing a rising line of five units or more—are included in column one—namely, those cases showing a rising line.

On examining Table No. IV we see that the conclusions suggested by Dr. Gibson hold good in only about one-half of the cases of this series. For example, of the 47 cases of general peritonitis, only nineteen, or less than half, showed a rising line of over five units, which is supposed to indicate a pretty severe lesion. Twenty-three of the cases of general peritonitis showed, on the other hand, a falling line, and this is supposed to indicate a mild process. Yet we must admit that no case of general peritonitis should be considered a mild process. Again, only fifty-eight, or a trifle over one-half, of the 101 cases of localized or spreading peritonitis showed a rising line, and of these 58 only 30 showed a rising line of over five points. In other words, less than one-third of the cases of localized or spreading peritonitis would be considered severe cases according to Dr. Gibson's chart, and more than two-thirds of the cases would be considered cases of good prognosis. By far the greater part of these cases, however, proved on the operating table to be severe cases.

Dr. R. H. Fowler, of St. Luke's Hospital in this city, reports* 278 cases of appendicitis. After a thorough examination of these cases he comes to the conclusion that the standard chart of Dr. Gibson offers the most advantages.

Dr. Noehren, of the German Hospital in this city, reports 69 cases.† He concludes that the estimation of the percentage of polymorphonuclears alone is more reliable than any method that has so far been suggested, also that a polymorphonuclear percentage of ninety per cent. or more indicates a severe process, which calls for immediate operative interference; a percentage below seventy-eight per cent. means a "safe" or mild process; a percentage between the two extremes speaks for the one condition or the other according as it approaches the one extreme or the other.

With the first conclusion, namely, that the percentage of poly morphonuclears is the most reliable method, the conclusions reached in this paper agree. But with the second conclusion namely, that operation is indicated, or not indicated, according as the percentage of polymorphonuclears is above ninety per cent. or below seventy-eight per cent.—we cannot agree. It may hold good in a certain number of cases, but the larger the series, the more exceptions occur, and it seems best not to draw any hard and fast rules from our blood counts and still less from our polymorphonuclear counts alone.

The writer wishes to thank Drs. McCosh and Eliot for permitting him to use their cases as material for this article.

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*Surgery, Gynecology and Obstetrics, Sept., 1908. "The Relation of the Lesion in Appendicitis to the Leucocyte Count."

†"The Value of the Differential Leucocyte Count in Acute Appendicitis." Annals of Surgery, Feb., 1908.

XVIII.

A CASE OF SYRINGOMYELIA WITH PARTIAL MACROSOMIA.

By M. G. Schlapp, M.D., Head of the Class of Nervous Diseases in the Dispensary

(*Reprinted from The Medical Record, May* 5, 1906).

Not many years ago, cases showing hypertrophy of one or more extremities, or other parts of the body, in connection with symptoms of syringomyelia, were described as acromegalia with accidental association of syringomyelia. These two groups of symptoms were looked upon as not having any special relationship to each other. It was not until recent years that this combination of symptoms was recognized as being caused by the same lesion, syringomyelia. This condition has been given a special name by Schlesinger—"Partial Macrosomia." For the enlargement of the whole hand, Hoffman and Marie have chosen the name "Cheiromegalia;" for the enlargement of the foot, Schlesinger has suggested the name "Podomegalia."

This hypertrophy usually begins in one extremity, spreading from there to the trunk, or jumping to the other extremity. It seems, sometimes, to involve the soft tissue alone; other times, and less frequently, it involves the soft and skeletal tissues. The length of an extremity is not found increased as often as is the thickness, nor does the length increase as much, when increased at all, as does the thickness.

In connection with the hypertrophy of the tissue, arthropathies are frequently found—thickening of bones about the joints, hardening of articular ligaments, and, as in the case described by Nolbandoff, softening of the bones.

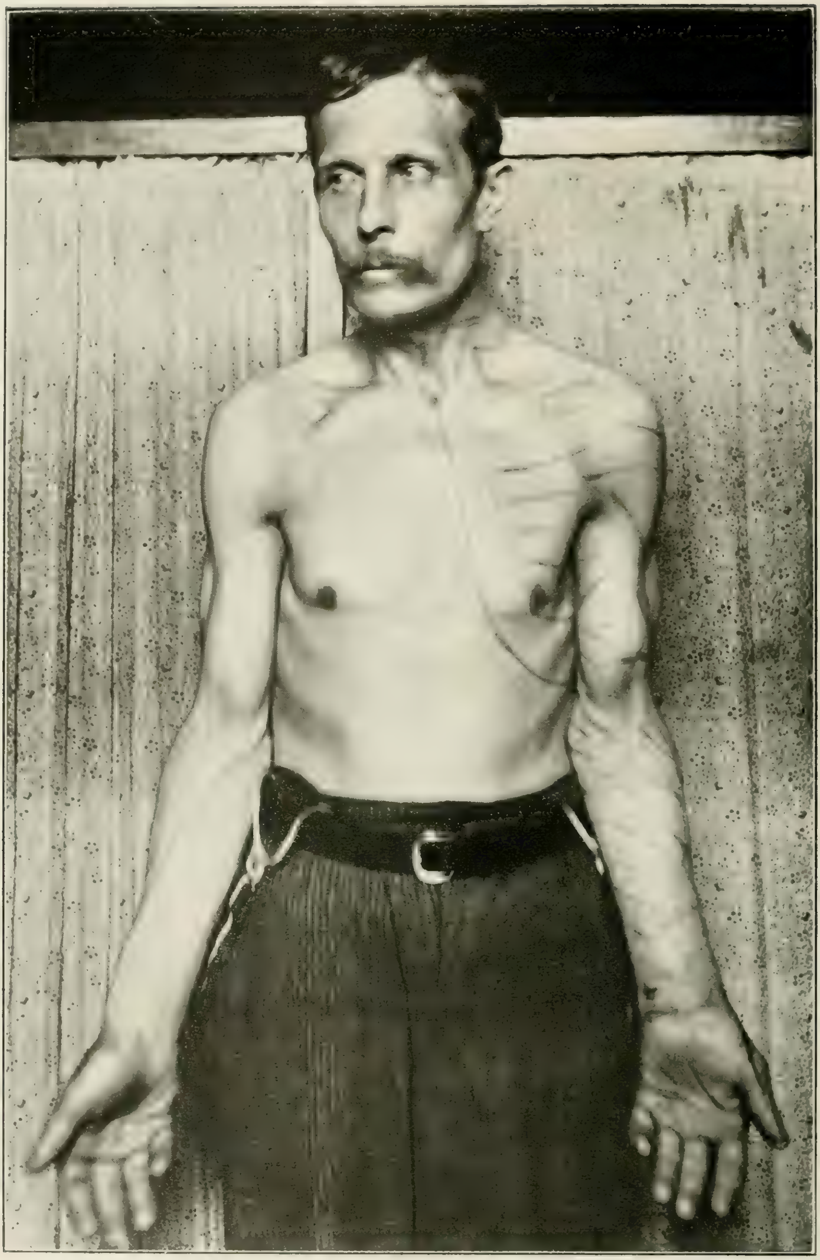

FIG. 1 A CASE OF SYRINGOMYELIA

ANTERIOR VIEW

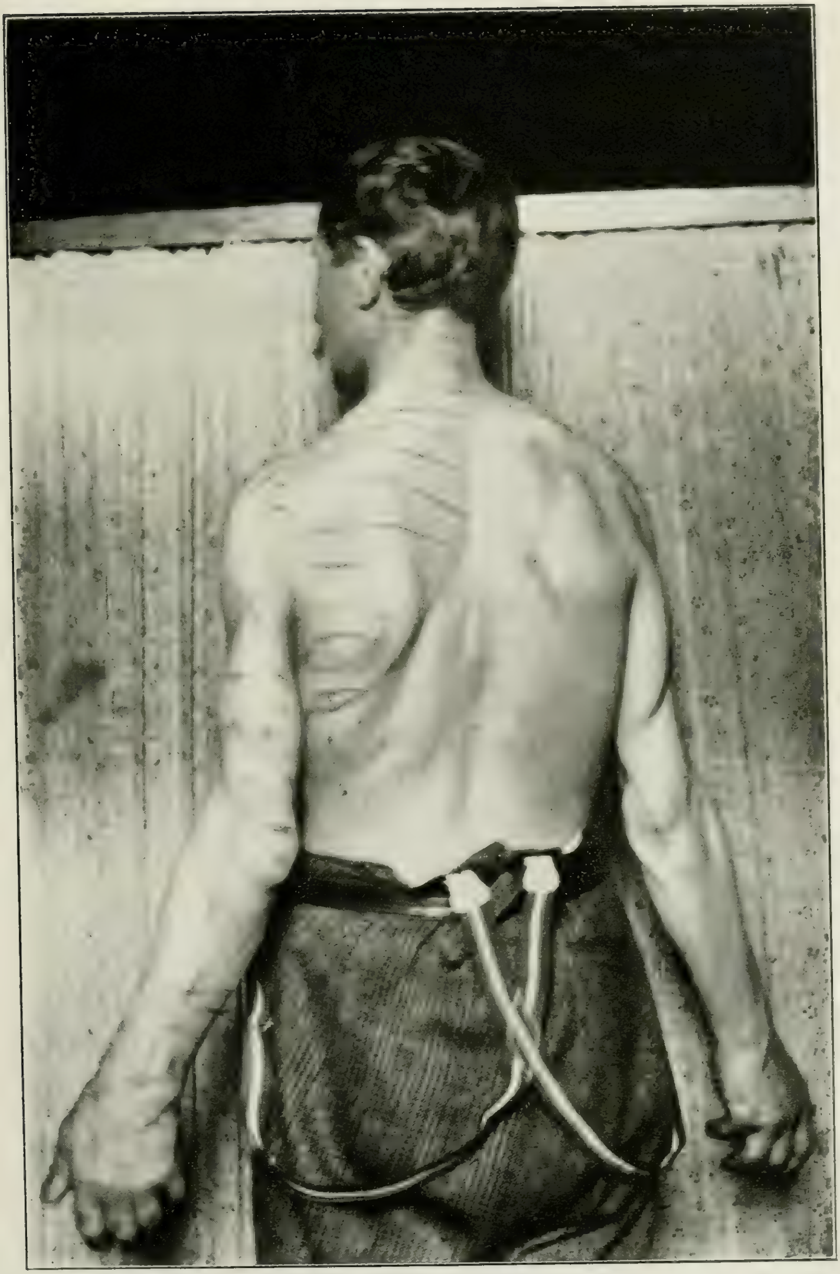

FIG. 2—A CASE OF SYRINGOMYELIA

POSTERIOR VIEW

The following case shows the unusual and interesting combination of hypertrophy of an extremity with dissociation of sensation, and with a number of other interesting symptoms.

G. H., male, thirty-eight years old, married, and has four healthy children. Father died of old age. Mother living and well, eighty-three years old. Three brothers and two sisters living and well. Two brothers died in infancy, cause not known.

Family history negative as to tuberculosis, nervous or mental diseases, rheumatism, etc. No deformities in family. As a child and boy, the patient always enjoyed good health. Fifteen years ago he had chancre with marked enlargement of the inguinal glands, which were very painful. He never had any further trouble from the chancre, but states that his wife had two miscarriages, and that one child died a few hours after birth.

The habits of the patient are good. Up to two years ago he was well. At this time he began to feel a heaviness in his left shoulder, and somewhat in the left arm. He paid no further attention to this condition until last December, about Christmas time, when rather suddenly his legs gave way, he felt "ill all over," as he expresses it, and went to bed. Immediately after this attack of indefinite illness, his left shoulder, arm and hand began to swell to about twice their normal size. He had no pain in the swollen arm and hand, but some in the joints of the right arm and hand. The arm remained swollen for about two or three months, after which the swelling began to subside gradually. Since this illness it has always been somewhat larger than the right arm and hand. Immediately after the onset of the illness in December, patient began to have attacks of dizziness, and during some of these attacks he would become totally blind in his left eye, the loss of vision lasting for about five minutes. These attacks of total blindness occurred four times, successive days. After the fourth attack the blindness was not complete. The loss of sight was confined to the lower half of the visual field; only the upper half of the left retina being involved. These attacks of partial blindness of the left eye gradually became less frequent, until now they occur about once a week, or once in ten days, accompanied always by dizziness.

During the past summer patient noticed that, while during the hot weather the right side of his face would perspire very freely, the left side would always remain dry. He was not so sure about the absence of perspiration on the left arm and chest, although he thinks they do not perspire so much as the right.

Status præsens: Well-nourished man, not much adipose tissue, but muscles well developed. Symmetry of face not disturbed, except that the left eye is drawn back into the fossa somewhat more than the right, which, however, does not show well in the photograph.

The left scapula has a lower position than the right, and recedes more from the vertebral column.

The left half of the chest and back, the left arm and hand, are larger than the right chest, arm, and hand. This is clearly seen in the accompanying illustrations (Figs. 1 and 2).

There is a slight double curvature of the spine; the upper convexity in the region of the sixth and seventh cervical vertebræ pointing to the left, the lower convexity at about the fifth, sixth, and seventh dorsal vertebræ, pointing to the right. The lower part of the body and the legs appear normal.

The measurement of the two arms and both sides of the body in the region of the chest are as follows: Middle of biceps, R., 28 cm.; L., 30 cm. Over largest circumference of lower arm, about 1½ inches below the elbow joint, R., 27 cm.; L., 28 cm. Wrist, over prominence, R., 18½ cm.; L., 20 cm. Hands, with thumb adducted, at base of first phalanx of thumb, R., 25 cm.; L., 26 cm. Over base of first phalanges of hands, thumb abducted, R., 22½ cm.; L., 23 cm. Length of middle fingers from base to tip, R., 11 cm.; L., 11½ cm. Length of ring finger, R., 10 cm.; L., 10½ cm. Length of little finger, R., 8 cm.; L., 8½cm. Chest, from spine to middle of sternum over the nipple, R., 45 cm.; L., 46½ cm.

There is complete loss to the pain and thermal senses over the whole left arm and hand, and on the surface of back and chest, neck, and back of head, as indicated by the shading in the illustrations.

On the chest, the area in which the thermal sense is lost is smaller than the area of analgesia, as indicated by the second line. Tactile and muscular senses not disturbed. No sensory disturbance in the trigeminal region, or on any other part of the body. The skin reflexes are present. The tendon reflexes of the legs, right arm, and jaw are slightly exaggerated. Tendon reflexes of the left arm are very much diminished.

The patient was placed in a hot air chamber and allowed to perspire freely. It was seen that on the left side of the face there was no perspiration (anidrosis), whereas on the right side there was profuse perspiration, the line of demarcation being sharply drawn down the middle of the face. The left arm and hand, the left side of chest and back were moist, whereas on the right side, on the same areas, the perspiration was very profuse.

The bones of the left wrist joint seem enlarged. There is permanent dislocation of the carpo-metacarpal joint of the thumb, which cannot be replaced. This dislocation is readily seen in the X-ray picture.

The strength in both arms and hands is equal, but in comparison to the muscular development the strength seems to be diminished. Both hands register 80 on the dynamometer. Nowhere is there seen any muscular atrophy or paralysis. A paresis of the left rhomboidei and levator anguli scapulæ, however, is found.

Eyes: Pupils equal; react to light and accommodation. Movements of the eyes normal. Visual field normal; normal fundus; physiological excavation of the papilla; left eye cleft smaller than right; left eye deeper in fossa than the right (enophthalmus).

Lungs: Normal.

Heart: Somewhat enlarged. Loud systolic murmur heard at apex, transmitted to all parts of the left chest. Mitral insufficiency. Blood pressure equal in both arms, measuring 120 mm. at systole, and 83 mm. at diastole.

Skin temperature equal on both sides. All other organs apparently normal. Taste, smell, and hearing normal.

For a year previous to the acute attack which the patient had in December of 1904, his left arm felt numb and not the same as did his right arm, although he did not know that the pain and thermal senses were absent until the examination was made at the clinic. It seems probable, therefore, that the loss of the pain and thermal senses has been gradually coming on for at least one year previous to the acute attack. This attack was, no doubt, brought on by a hemorrhage in the area of gliosis, or in the necrotic tissue, the result of a central gliosis (for such I take the lesion to be). It would appear that the hemorrhage confined itself to the intermediate gray matter at the base of the left anterior horn throughout a number of segments, first cervical to about the sixth dorsal. Two sets of symptoms resulted from this hemorrhage: irritative and paralytic.

As irritative symptoms, must be considered the attacks of blindness of the left eye, and, with this blindness, the dizziness. These attacks were no doubt caused by an irritation to the sympathetic centres in the cervical region, causing spasms of the blood-vessels of the left retina, with resulting blindness, and spasms of the small vessels in part of the brain, with resulting dizziness.

These irritative symptoms have gradually subsided since the onset of the acute attack. An interesting feature, to which attention should be directed, is that when the irritation was most marked, all the blood-vessels of the retina were involved in the spasm, but as the irritation subsided the spasm involved only the blood-vessels of the upper half of the retina. The correct interpretation of this peculiar phenomenon is, no doubt, that the motor impulses from the intermediate gray matter of the cord passing through the cervical sympathetic to the upper half of the eye, come from cells that have a different position from that of those cells which supply the blood-vessels of the lower half of the retina.

With the paralytic symptoms must be classed the anidrosis of the left side of the head, the enophthalmus (paralysis of M. orbitalis), and the œdema of the hand, arm, and shoulder, caused by the paralytic dilatation of the blood-vessels in these parts. It is very probable, likewise, that an enlargement of the area of analgesia and loss of the thermal sense took place after the hemorrhage, although this could not be demonstrated, as it is impossible to know how large the area was in which the pain and thermal senses were missing before the acute attack.

Before the appearance of the œdema in the left arm and shoulder, the patient is positive that there was no difference in the size of both arms. It seems, therefore, that the hypertrophy began to develop some time during the existence of the œdema. This being the case, is there any connection between the œdema and the subsequent hypertrophy? I am inclined to think that there is, although it would have been desirable and important to know whether all tissues were involved in the process of hypertrophy, or whether there is only increase in the connective tissue as the result of katabiotic changes. I suggested to the patient that pieces of different tissues of the arm be removed for histological examination, but this was refused. It seems that the bones are involved as well as the soft tissue; not so much in the increase in their size, as in the greater opacity of the affected bones, possibly due to an abnormal amount of salts deposited.

In many of the reported cases of partial macrosomia, the hypertrophy is either preceded by phlegmonous conditions with œdema, etc., or by œdema only due to the paralytic dilatation of the blood-vessels, as in the above case. In the cases where this factor has not been mentioned, it is possible that it has been overlooked, as no importance was attached to it.

Before endeavoring to point out the connection between the œdema and the subsequent hypertrophy in the above case, it is perhaps advisable to state very briefly the prevailing opinion held at present concerning the cause of hypertrophy of tissue.

It is generally conceded that a living cell is capable of developing three physiological activities: functional, nutritive, and formative. Formerly it was supposed that these three activities were the result of a direct stimulation. The functional activity being the result of the weakest, the formative activity the result of the strongest, stimulation. This, as has been pointed out by Weigert, cannot be the case, for the functional activity is a translation of the energy stored in the cell body and nucleus, into the specific energy of the cell in question, and attended with a breaking-down of the cell element. The nutritive and formative activities are the diametric opposite of this—a replenishing of the broken-down elements and growth or multiplication of the cell. The former, or functional activity, has been given the name "Katabiotic process;" the latter, or nutritive and formative activities, the "Bioplastic process."

In the undeveloped individual, as in the undeveloped cell, the relation of different parts of the whole, to one another, is such that an equilibrium throughout the whole does not exist, or in other words, the tissue tension has not reached the point where it inhibits the bioplastic processes, so that they will continue until this equilibrium is established, after which the bioplastic energy will be forced into a dormant state. Should this tissue tension, either in the individual cell, or in the individual, as a whole, again be disturbed, the bioplastic process will again flare up, and growth will continue until the amount of tissue tension develops, which will again inhibit growth. The equilibrium in the individual cell is disturbed every time a cell is stimulated physiologically, whereby substances are removed from the cell (katabiotic process), but which can be, and are, normally replaced readily by the nutritive or bioplastic process, thereby reëstablishing the equilibrium. It often occurs that by a pathological irritation more intense than a physiological stimulus, the tissue tension is disturbed to such an extent that not only the nutritive but also the formative activity will be liberated, and we will then have cell division and growth beyond the replacement of normally disturbed tissue or hypertrophy. This growth of tissue is due to the bioplastic process.

There is, however, another way by which the amount of tissue can be increased, and that is by the katabiotic process. If a muscle cell is stimulated it will contract, thereby developing measurable energy and heat; if a gland cell is stimulated, it will secrete a substance characteristic of itself. If a connective tissue cell is stimulated it will deposit an intercellular substance (connective tissue fibres), or, in case of osteoblasts, calcium deposits in bones, the result of the katabiotic process. So it is evident that we can have increase of a certain kind of tissue (connective tissue) as the result of a katabiotic process.

In the above case, is it not probable that the hypertrophy is the result of a disturbance of tissue tension, which in turn was brought about by the œdema caused by the paralytic dilatation of the arteries in the tissue involved?

Ribbert has expressed the opinion that tissue tension can be disturbed by a simple hyperemia, the result of which is an hypertrophy of the tissue involved. A pupil of Ribbert, E. Feurst, has taken up this subject, and he succeeded in producing an hyperemia with a subsequent hypertrophy of the tissue involved, by exposing tissues to low and high temperatures. Feurst, however, is of the opinion that it is not the hyperemia alone that causes a disturbance of tissue tension, but that pathological changes in the cells, brought about by exposure to the low or high temperature, is a factor in disturbing tissue tension. In the above case the factor of pathological changes in the tissue due directly to the effect of the low or high temperature, in bringing about a disturbance of tissue tension, can be excluded; instead, we have a paralytic dilatation of the blood-vessels with œdema caused by a lesion lying remote from the tissue hypertrophied, and therefore in no way directly affecting it. This is, therefore, that ideal condition to which Ribbert has referred as being so difficult to produce experimentally, viz., the production of an hyperemia in a tissue, without injuring the tissue directly by the agent which produces the hyperemia.

The present case may also bear upon the theory of special trophic nerves, but it seems to me that there is not sufficient evidence in support of this theory to call for a discussion of it in this connection.

The study of this case is by no means complete, as it is impossible for me to ascertain the nature and extent of the hypertrophy, as histological sections of the tissue could not be made; but it seems probable that we have a tissue hypertrophy, the result of the bioplastic, as well as the katabiotic process.

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XIX.

SUBCORTICAL CYST AND FIBROMA DUE TO TRAUMA PRODUCING JACKSONIAN EPILEPSY, CURED BY OPERATION.

BY MAX SCHLAPP, M.D., NEUROLOGIST TO THE OUTDOOR DEPARTMENT
AND
JAMES J. WALSH, M.D., PH.D., OF NEW YORK.

In the summer of 1902 a young man, nineteen years of age, presented himself at the Dispensary of the Presbyterian Hospital, complaining of weakness in his arm and leg. He had been employed as a grocer's boy for some years, until the increase of weakness of his arm and leg made it impossible for him to continue at this occupation. When he came under observation he gave a history of having had about a year previously certain convulsive symptoms, especially on the left side of his body, and especially in his left arm and the corresponding side of his face. The description given of these evidently pointed to the fact that he was suffering from true Jacksonian epilepsy. Further inquiry into his history seemed to indicate that his condition was very probably traceable to an injury about five years before.

His family history was negative, both as regards tuberculosis and the occurrence of neoplasms. His own previous history, with the exception of the injury to his head, had very little that was of interest before the beginning of his present illness. He had whooping cough and measles as a child, but without any sequelæ. He had never used alcohol to excess, nor, indeed, indulged in it to any extent at all, and he denied all venereal infection. His mother said that he had suffered from malaria and rheumatism, but the symptoms she gave of these diseases made it very dubious whether they had really been present. The boy had grown rather rapidly between twelve and fourteen, and as a consequence had suffered from that tired feeling which, a few years ago at least, was supposed to indicate malaria. He had begun hard work rather early in life, and occasionally complained of pains around his joints, which were worse on rainy days, and this was supposed to justify the diagnosis rheumatism.

There is no direct history of either of these affections; the patient has never lived out of Manhattan Island, and is very little likely to have contracted real malaria, and he did not have the red, swollen joints of true rheumatism.

A very interesting and important item of his history, however, is that five years ago, while working on a new building, a barrel fell from the sidewalk above his head, a height of about five feet, and struck him just above and behind the right ear. He did not lose consciousness at the time, and refused to permit the doctor whom he visited after the accident to put any stitches in the scalp wound which occurred at the time. The wound healed perfectly, leaving scarcely any trace except a linear scar on the scalp, and until very recently he has had no further symptoms pointing to any serious injury of the head at that time. Some three years after the accident mentioned, however, just after going to bed one night, a sharp pain, which began in his left hand, crept up his arm to his shoulder, while at the same time there was a twitching of his fingers. After a while his wrist and then his arm and shoulder were drawn up, and finally a pain and a sensation were felt, as though his face on the left side were contracted. After this he lost consciousness, remaining unconscious for some twenty minutes to a half hour.

He then awoke, feeling, as he says, perfectly well. On closer questioning he confesses that there was a tired feeling, but of this he didn't make much account. In general it may be said, with regard to him, that he is one of those phlegmatic individuals who do not notice pain or discomfort very much, and the only thing that bothered him really was the weakness of muscles which began to develop. After this first seizure there was no paralysis, stiffness or pain in his arm or face. Just before he became unconscious, however, he thinks he remembers that the spasm became very severe, and his whole arm was stiff, that is, was in firm tonic contraction. Occasionally after this he had slight pains in the wrists, arm and shoulder, with some muscular spasm. These came on in attacks, which recurred more and more frequently. At the end of two weeks they were recurring nearly every day, though they did not produce any special disability.

After two or three months he had an attack exactly similar to the first one, while sitting quietly in a chair at his work. This attack lasted only fifteen minutes. On awaking he walked home, a distance of several blocks, without delay, and without discomfort, though he felt weak on his left side and limped at first, but only for a few minutes, when he regained his strength entirely. For a month after this, except for the slight twinges of pain, with occasional twitching, which recurred every day or so, he had no further symptoms of his affection.

Then, one day, while pushing a grocer's cart, he felt the pain and spasm beginning in his left arm, and realizing that it was more severe than usual, and that he was going to have one of his attacks, he ran toward a stoop to sit down. Before he got there, however, as he says himself, he began to go sideways, bumped into a wall and fell down, losing his senses. This attack lasted more than half an hour. His left side felt weak after this, his left leg dragged a little, and he staggered toward this side. These symptoms lasted, however, only for a short time. Then he was able to go on with his work again without any bother.

This attack occurred two years and eight months ago, and he has not had a similar attack since. He had slight attacks of pain and twitching for some time afterwards, but these gradually grew less noticeable and less frequent, and stopped entirely over a year ago. For the last three months, however, a new set of symptoms has developed, and he and his friends have noticed that he throws his left leg awkwardly, which produces a decided limp, and his arm has been gradually getting weaker, until now it is so paralyzed as to be useless.

About two months ago he suffered from a very severe headache. It came on at night while he was asleep, without known cause, grew steadily worse until midnight, when he suddenly vomited violently. After vomiting the headache became somewhat better, and entirely disappeared before the next morning. At first the pain was all over the head; as it grew more severe it seemed like an iron band about his head. After the vomiting he felt the pain almost exclusively in his temples and eyeballs. One week later he had another headache of the same kind. This came on about the same time at night. He vomited about midnight once more and the pain in his head left him in the early morning. Six weeks later there was a third attack of headache just like the other two, only that it continued to grow worse until eight in the morning, when he vomited, and then the headache disappeared within a short time.

This was his history when he came under our observation, asking for treatment for his headache, for the weakness of his left leg, and for almost complete inability to use his left arm. We found him well nourished, not at all anæmic, and his tongue, moist and clean, was protruded in the median line, though there were some fibrillary tremors present in it. His post-cervical lymphatic glands were enlarged, his pulse full, soft and regular, his heart normal in size and in action, but with a faint blowing systolic murmur at the apex. Careful physical examination of all his other organs showed no abnormalities except in his nervous system.

His pupils are equal and react to light and accommodation, though there is some evidence of facial paralysis on the left side. He talks somewhat thickly, but there is no alteration in his faculty of speech. His left arm is almost completely paralyzed, though there is some small amount of power left in the shoulder muscles. The arm is quite rigid in adduction and with the forearm flexed. The muscles are soft and flabby, but evidently only from disuse, as they show practically no wasting. The muscle and tendon reflexes in the arm are increased. Whatever muscular atrophy is present is more marked in the forearm. His left leg shows distinct loss of power, though he can move it in every direction. The muscle and tendon reflexes in this limb are exaggerated, and Babinski's sign is present. Ankle clonus could be elicited without difficulty.

Careful examination of his eye-grounds was made and marked optic neuritis was found in each eye by Dr. Parker, who also found the vessels tortuous and dilated with choroidal atrophy in the region of the nerve-ending. The optic disc in each eye was swollen about two millimeters. In general the pathological conditions present were found to exist to about the same degree in both eyes.

Some of the most important symptoms were found in the sensory disturbances in the affected arm and hand. The deep muscular disturbance was very marked, and he could not tell the positions of his fingers, and was not able to state with any confidence the position of his hand or the amount of angular movement in his elbow. His tactile sense in his fingers was extremely blunted, and below his elbow was distinctly less than on the other side. Pain and temperature senses were not disturbed. There was distinct astereognosis, and such familiar objects as a pencil, a knife or a coin, could not be recognized when placed in his hand.

The diagnosis of the case, as made by Dr. Schlapp, was cranial neoplasm; the reasons for this diagnosis were to be found in the characteristically developing symptomatic picture, to be traced in the history and in the present condition. The original injury, followed after some years by Jacksonian epilepsy, with distinctly focal symptoms, then later the severe attacks of pain, followed by vomiting, without any special reason for it on the part of the digestive tract, and then the gradually developing weakness of the arm and the leg, with some involvement of the face, with the choked discs and the sensory disturbances, all pointed definitely to the existence of an intracranial neoplasm. In so young a patient it seemed eminently advisable to try what could be accomplished by operation.

The outlook after operation depended, however, to a very large extent, on the nature of the tumor that might be present. The very slow growth, taking years for its increase to such a size as to produce symptoms, pointed either to the existence of a glioma, or a very slowly-forming cyst. The injury might have given rise to scar tissue, the irritation of which would eventually produce gliomatous growth, but it was more likely to have produced cyst formation, and it was hoped that this was the pathological condition that would be found, since the prognosis, after the removal of a cyst from the cerebrum, is much better than that of a glioma, and is, indeed, as a rule, very favorable.

The position of this tumor was evidently in the posterior central convolution back of the second frontal convolution, not exactly in, but in the neighborhood of the arm and leg centres, and volving them indirectly by pressure rather than directly.

Accordingly, he was referred to the surgical wards of the Presbyterian Hospital, where he was operated upon by Dr. Woolsey. The usual incision for the examination of the area near the fissure of Rolando was made, and a horseshoe-shaped flap of the scalp turned down. The opening through the skull was made by means of an electric saw. The pericranium and bone were lifted in a single flap. As the scalp was rather vascular it was found necessary to tie a rubber tube as a tourniquet around the skull below the field of operation. This controlled the bleeding very well, and no further difficulty was experienced from the severed vessels.

As soon as the flap of skull was lifted, the brain bulged through the opening, somewhat above the level of the skull, though still, of course, covered by dura and retained by that membrane. The color of the bulging part was rather yellow, and the usual pulsation noted when normal brain substance is exposed was not present. An incision was made into the dura, and the brain bulged still further through it at the base of the flap, gradually becoming bluish in color. Shortly after the incision in the dura the bulging brain tissue ruptured, discharging a stream of yellowish, slightly turbid fluid, about four or five drams in amount, which spurted some eighteen inches high. This was found to come from a cyst close under the surface of the brain. After this evacuation of the cyst the brain began to pulsate. The flap of dura was then elevated, bleeding points in the brain tissue were secured with fine catgut on a curved needle, and the opening in the cyst wall enlarged and the cyst explored with the finger. It was found to be two inches in diameter, of oval shape, and containing within it a pedunculated, nodular tumor of medium consistency, more or less spherical, about one and a quarter inches in diameter, and attached to the inner cyst wall at the upper posterior portion. After enlarging the opening this tumor was easily removed, shelling out without noticeable bleeding or laceration of tissues.

It was considered advisable then to make a small opening in the edge of the bone flap, through which to allow a small strand of drainage tissue to be carried. The wound was then closed, the dura with catgut and the scalp with silk. The condition of the patient remained good during the operation. The pulse, which was 120 at the beginning, gradually rose to 155, but remained of fair quality during the operation, which lasted an hour and a quarter.

The etiology of the cyst thus removed is not difficult to understand. The severe injury to the head five years ago caused either the rupture of a small artery with hemorrhage, though not of large size, or thrombosis, and interrupted the circulation in a small portion of the subcortical region, with consequent softening. This, of itself, was not large enough at the time to produce any focal symptoms.

Following the softening of the tissue there must have been a proliferation of the connective tissue as well as from around the blood-vessel. This process eventually led to the formation of the wall of fibrous tissue about the area which had become softened, separating it completely from the normal-brain tissue in the neighborhood. In time the broken-down tissue within the cyst, the detritus of degenerate cells, was carried away by the fat granule cells and also epithelioid cells, leaving the fluid in the enclosed connective tissue cavity quite clear. From the fibrous tissue wall the tumor in the case developed. In the course of its development the pressure within the cyst was gradually increased, until after some time pressure symptoms became noticeable.

That this cyst was not of congenital formation, due to an anomalous pinching off of some portion of the lateral ventricle, a not very unusual incident, or to some other malformations of the ventricles during embryonic life, is clear from the fact that in that case it would have been lined by ependyma cells. The existence of a fibrous tumor within the cyst showed that it was not ependymous in origin, since a tumor springing from that sort of tissue would have been a glioma. As can be seen from a microscopic section of the tumor, it is very likely developed from the cyst wall after this had already been formed. The cortex of the brain was intact above the tumor so that it was not an ingrowth from the pia. This tumor was connected with one portion of the lining of the cyst and derived its nourishment, being rather freely supplied with blood-vessels, from this part. The tumor was not of very firm consistence, but was distinctly fibromatous in character, and even appeared so to the naked eye on section.

It seems probable that there will be no recurrence of the symptoms. Much of the pressure exerted by the cyst was probably due to the fact that the growth of the tumor gradually pushed the increasing fluid against the cyst wall, thus exerting pressure on the surrounding brain tissue. It is very probable that the absence of serious lesions in the brain tissue was due to the fact that the fluid within the cyst acted somewhat as a water cushion in neutralizing the action of the tumor upon surrounding tissue. The pressure, too, in this way was equalized all over the cyst, thus accounting for the gradual, slow developing of the symptoms.

The patient recovered from the anæsthetic with only slight nausea and vomiting, and though there was a profuse serous discharge it was surgically clean and remained in excellent condition. The temperature reached 102.4° F. the day after the operation, but the patient seemed to be much brighter than before. He answered questions promptly and was able to move the paralyzed arm and leg better than for months. He could put his left hand above his head, though this had been impossible just before. The grip was rather feeble in the left hand as yet, and his muscular sense was disturbed, as he could not recognize the position of his left hand when his eyes were closed. He also had astereognosis, that is, he was incapable of recognizing the character of an object held in his left hand when his eyes were closed. The second evening after the operation he complained of severe headache, and there was a loss of the motion in the left arm. The wound was dressed, and there proved to be a small bloody discharge. The next morning, however, his headache was gone and motion in his arm and leg had returned. There had evidently been an obstruction in the drainage, blood and serum having filled out the cyst again, thereby causing pressure and consequently paralysis of arm and leg.

Since the first day after the operation there has been no disturbance of the favorable course of the disease. His temperature has not been above 101° F., and his movements have grown steadily stronger and more capable of direction. It is especially noteworthy that he uses the fingers much better from day to day, and that his sensations are improving, though he still has astereognosis. His muscular sense is much better than it was, and his pain and temperature senses are practically normal. Three weeks after the operation the patient was allowed to get up, and was able to walk quite well, though there was some incoördination of movements in his left leg. At this time he was able to recognize the position of his left thumb and first finger when they were moved with eyes closed, though his muscular sense in the other three fingers was still imperfect. The Babinski sign was still present.

When he was discharged, just four weeks after the operation, the general condition was good, there was no sign of facial paralysis, and the motions of his left arm and leg were practically normal, though his muscles were weaker than in the right arm and leg. These muscles have grown much stronger than they were before the operation, but have still not regained their normal size. The wound in his skull is closed, all but a small sinus, not more than a centimeter in depth. The bone flap united very thoroughly, and there is no depression in the skull.

The patient has been seen within the last few weeks and he is now driving a brick wagon, and says he feels absolutely no inconvenience from the rather serious experience through which he passed. He is able to use his hands with equal force, and none of his muscles seem to be lame. He never suffers from headache, and has no vomiting and no nausea. He is, as we have said, rather phlegmatic in his character, and it is possible that his rejoicing over the fact that he is able to get back to work may suggest to him that he is quite as well as ever.

There seems no reason, moreover, to doubt what he says from his appearance, or from his gait, or from what fellow workmen say of his capability for using his hands and legs. This would seem to be one of those very fortunate cases, where, notwithstanding the existence of serious symptoms, operation led to the removal of the tumor before any serious damage had been inflicted upon the nervous system. It illustrates how much may be accomplished by localizing diagnosis and timely surgery, for without operation this young man would have been rendered incapable of earning his livelihood for the rest of his life, the span of which, moreover, would not have been very long. With the gradual increase of intracranial pressure that had taken place during the last year, it would not have been a question of much time before a fatal termination would have been imminent, because of interference with important vital functions. The complete palsy which had existed for some time in the arm and leg might have discouraged the idea of operation, because of the fear that degeneration of nerve fibres had already taken place, and the eventual outcome would not be very favorable. The patient has, however, been left practically without a mark of his previous illness.

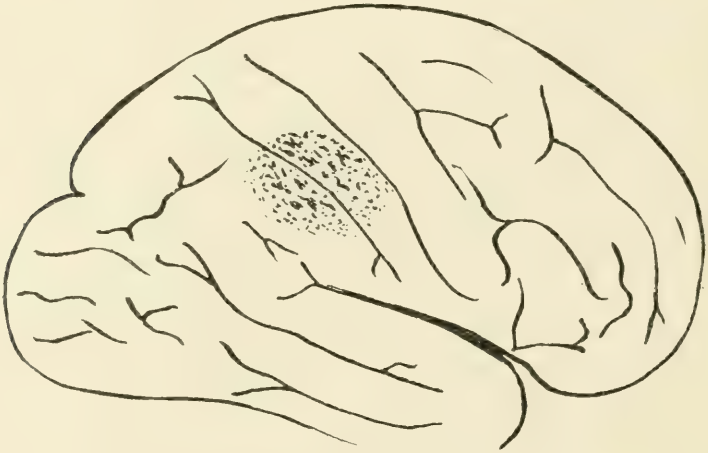

Diagram Showing Location of the Cyst.

In conclusion can be added that this case is interesting on account of the definite location of the lesion, although most of the symptoms were produced by the pressure upon the immediately surrounding tissue, evident by the complete recovery of the patient. The cyst was found to be in the posterior central convolution, back of, and pressing upon, the arm centre, and upon the fibres coming from it on their way to the internal capsule. The fibres from the leg centre, on their way to the internal capsule, must have been affected by the pressure, but not so much as those from the arm centre. The location of the cyst is shown by the accompanying diagram.

The motor symptoms can easily be explained by the pressure on the adjoining motor centres and fibres involved. The pressure at the beginning of the lesion, involving the motor cortex of the arm, produced the Jacksonian attacks; later, during the development of the case, the pressure interfered more or less with the function of the motor fibres, causing a cessation of the Jacksonian attacks. The cortical centre of the leg was not so much involved, as there were no clonic contractions of the leg muscles.

There was no disturbance of pain or temperature sense. The muscular sense was very much disturbed as far as above the elbow; somewhat less the tactile sense. Astereognosis was complete in the hand. All these symptoms have disappeared with the exception of the loss of the muscular sense of the little finger.

To enter into a detailed discussion upon the probable location of the cortical centres of the disturbed sensory functions would carry us beyond the scope of this article.

XX.

THE EYE SYMPTOMS OF SPORADIC TRICHINOSIS, WITH REPORT OF CASES.*

By Frank Judson Parker, M.D., Ophthalmic Surgeon to the Out-Patient Department.

(*Reprinted from The Medical Record, August* 3, 1907).

Our knowledge of this interesting disease dates from the publication by Zenker, of Dresden, of his famous theory of the parasite as a pathological factor in human beings. In performing an autopsy on a nineteen-year-old girl who had entered the hospital and died, supposedly, of this disease, he found numerous trichinæ in the intestinal tract and in the muscles; the intestinal lesions of typhoid fever were absent. A few weeks before the girl had been taken sick after eating pork. The source was traced and numerous other cases discovered. Hardly had this case been reported when reports of epidemics came from North Germany. Previous to this date there had been numerous reports of the finding of the parasite at human autopsies. In London, Peacock, in 1828, and Hilton, in 1833, had found encapsulated trichinæ in the muscles of man; Paget, in 1835, found them in an Italian who had died of tuberculosis, and recognized them as the entozoa which Owen had described as trichina spiralis. Leidy, of Philadelphia, in 1847, found it in the hog; this opened the way for Zenker's classic work. Kirchenmeister and Virchow, in 1859, by a long series of experiments, showed that the trichinellæ became adult in the intestine a few days after the entrance of the larvæ, and that the females were viviparous. Previous to this time they had been regarded as harmless guests of man. Soon after introduction into the intestine, the encysted trichinæ escape from their capsules, which are destroyed by the gastric juice; they then enter the duodenum and jejunum, where they become adult, copulation taking place in two days; the males die and the females bore deeply into the villi or through Lieberkühn's glands, penetrate into the mucous membrane, and thus reach the lymphatic spaces, here depositing their young. The newly born larvæ measure about one millimeter in length. These larvæ are carried by the lymph stream, or the blood, and are distributed throughout the body. The conditions necessary for their further development are found only in the transverse striated muscular system. On the ninth or tenth day after infection the first trichinæ have reached their destination and further invasions are constantly taking place, because the intestinal trichinæ live from five to seven weeks and continue to reproduce. It is the invasion of the muscles by the migration of the new brood which causes the inflammation manifested by severe pain, fever, and œdema about the eyes. The trichinæ in the encysted condition remain alive and capable of development for many years, the subsequent invasions producing more severe symptoms.

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* Read before the Section of Ophthalmology, New York Academy of Medicine, October 15, 1906.

The Germans have been the greatest sufferers from this disease, and a report from their Bureau of Animal Industry from 1860 to 1898 gave 14,820 cases, with a mortality of 835. Their careful inspection of pork has greatly reduced the number of cases, and up to 1898 no case in Germany had been traced to American pork products. One of the most glaring disclosures of the recent food investigation was the fact that there was no inspection for trichinosis in hogs intended for sale in this country, a microscopic inspection being maintained solely for the benefit of Europe, and pork that was found unfit for exportation was being sold for food in this country. Trichinosis in man has been considered a rare disease in this country, only nine hundred cases being reported since 1868. That the disease is far more prevalent here than has been suspected is proven by H. U. Williams, who reported in 1903 that out of 505 autopsies of persons in whom the disease had not been suspected during life 5.34 per cent. had trichinosis. In 1897 a case in Dr. Osler's clinic, with suspected typhoid fever, was found to have a leucocytosis with increase of eosinophile blood cells. Examination of muscle tissue showed numerous trichinæ, and further examination showed the blood examination to be of the greatest diagnostic importance in recognizing this obscure disease. Osler has reported seven cases of trichinosis, all of which showed a marked leucocytosis and eosinophilia. Cabot regards this as a constant symptom, and states that it has reduced trichinosis to the list of diseases which are easy of diagnosis. Ewing, on the other hand, states that while increased eosinophilia should always suggest trichinosis, this has long been known to accompany other conditions. Of thirty-seven cases reported up to 1903 thirty-one had eosinophilia from 20 per cent. to 86 per cent., and there was no relation between the amount and the severity of the case. The eosinophilia varies to a great extent from day to day. Vickery reported a case that one day showed 23 per cent. and two days later 2 per cent., and in the following two days 37 per cent.; it also continues high long after recovery.

There are a large number of diseases in which an increase of the eosinophiles takes place, usually with a small percentage, but the conditions most likely to be confused with trichinosis are those due to other intestinal parasites. A differential diagnosis presents little difficulty, with that exception. Packard, in reporting a case in 1897, speaks of the marked œdema of the eyelids and surrounding skin, especially above the brow; this subsided after three or four days; there was no involvement of the conjunctiva. The same year Oliver reported the eye examination of a case reported by Brown as follows: "Vision and accommodation normal, pupils equal, and respond freely to light and accommodation; marked hyperphoria for near and far; fundus normal, except a small striated hemorrhage overlying the inferior temporal vein just beyond the primary bifurcation in the left eye; fields normal; the only gross ocular change being the disturbance in the muscular equilibrium in the vertical meridian."

Osler reported five cases in which there was œdema of the eyelids, and he considers this as being one of the three characteristic symptoms—the other two being leucocytosis with eosinophilia, and the muscular pain and swelling.

Dr. David Bovaird, Jr., in a recent report of ten cases of sporadic trichinosis at the Presbyterian Hospital, noted the marked œdema of the eyelids in nine of them; in three it was the earliest symptom. Five had hyperemia of the conjunctiva, and one case had a mucopurulent discharge. He regards the œdema as one of the most characteristic symptoms.

The following six cases, to which I ask your attention, came under my observation at the Presbyterian Hospital in the spring of 1906:

Case I. Miss C. K., a trained nurse, aged thirty; single; consulted me on January 5, 1906; was of German parentage; lived in New York since seven years of age; general condition excellent; family history negative; had frontal headache after use of eyes. I ordered a correction of plus spherocylinders to be worn constantly. Her eye muscles were normal. I saw her again on January 25, and she had been free from the headache since wearing the glasses. I next saw her on February 13 following. She had marked collateral œdema; tenderness of the globes; diplopia on looking down, and occasional attacks of nausea. Examination showed vision 20/20 each eye with correction (homonymous diplopia with red glass); right hyperphoria, 1½°; esophoria, 2°; continual headache and muscular pain. This continued with increased severity, and on February 23 she was admitted to the Presbyterian Hospital on Dr. James' service. Blood count showed an eosinophilia of 20 per cent.; collateral œdema, ocular conjunctiva injected, eyes tender to the touch and painful on rotation; pupils reacted to light and accommodation. The diagnosis of trichinosis was confirmed by sections of lumbar muscles, showing the characteristic interstitial myositis. Discharged from Hospital on April 5. I last saw this case on May 22. She had been free from headaches and her eye muscles were normal.

CASE II. Miss M. W., aged twenty-five; admitted to Presbyterian Hospital on January 19, 1906; a domestic; general condition good. Four days ago was taken with severe pain in both eyes; pain increased on rotation. The following evening the eyelids began to swell and face was flushed; following morning the lids were closed from the increased swelling, both eyes very red and painful; had no muscular pain until two days following the pain in eyes. On admission to the Hospital eyelids were swollen; slight œdema of the conjunctiva; subconjunctival ecchymosis of the lower half of each eye; eyes very sensitive to touch and painful on rotation. Blood examination showed 30 per cent. of eosinophiles; this was 49 per cent. on January 27 and 52 per cent. on February 7. Section from gastrocnemius muscle showed trichinæ. February 13 symptoms had disappeared except slight headache. Patient discharged.

CASE III. W. B., German, aged forty-four years; admitted to Hospital May 30, 1906. One month ago had severe abdominal cramps, vomited frequently; pain and anorexia continued. Eight days ago noticed puffiness of eyelids; a steady pain seemed to be in back of eyes; rotation in any direction caused severe pain. Two days ago had pain in throat and hoarseness. On admission eyelids were swollen, ocular conjunctiva injected, globes painful on pressure and rotation. Blood examination showed an eosinophilia of 18 per cent. Section of muscle from leg showed large numbers of encapsulated trichinæ.

CASE IV. Miss V. B., aged eight years; a child of patient III. Was admitted to Hospital on May 30, 1906. Three days ago had slight headache, lassitude, and swelling of eyelids; no gastro-intestinal symptoms or muscular pain. On admission had marked swelling of lids, conjunctival injection; no muscle tenderness or pain on motion at any time; eosinophiles, 35 per cent.

CASE V. Mrs. M. B., German, aged 25; admitted to Hospital May 30, 1906. A large, well-nourished woman. Seven days ago had distressing pains in legs and back; had swelling of the eyelids and severe pain in head and eyes. On admission had injection of the ocular conjunctiva, tenderness, and painful rotation; blood examination showed an eosinophilia of 18 per cent.; urine contained no albumin and a few epithelial casts. On June 2 ophthalmoscopic examination showed beginning optic neuritis in each eye; veins enlarged. On June 7 there was a marked optic neuritis, with œdema of the retina in each eye; veins large and tortuous, arteries small, a small hemorrhage just above the macula in the left eye. The urine showed a faint trace of albumin and a few granular casts and pus cells. On June 14 the retinal œdema and neuritis was less, several small hemorrhages in the superior temporal field of the left eye; no hemorrhages in the right eye. Condition of the urine same as on the 7th. This patient improved steadily and was discharged on the 27th of June. The optic neuritis had disappeared, and there were only slight traces of the hemorrhages. The fundus lesion in this case was characteristic of acute nephritis, which was probably caused by the intestinal toxæmia.

CASE VI. A. D., a school girl; Italian; admitted to Hospital on March 29, 1906. Twelve days ago was taken with severe pain in the muscles and swelling of the eyelids; on admission to the Hospital she had collateral œdema with injection of the ocular conjunctiva. Blood examination showed an eosinophilia of 18 per cent. Section of muscle from calf of leg showed immense number of trichinæ and myositis.

The incubation period in these cases was from one to two weeks, which is the time required for the immature parasites of the infected meat to reach maturity and reproduce their embryos and for the embryos to leave the intestinal tract and invade the muscles. The invasion is marked by a variety of symptoms, such as loss of appetite, exhaustion, fever, headache, abdominal pain, vomiting, muscular pain and tenderness, swelling of the eyelids, and pain on pressure and rotation, eruption on the chest and back. In summing up the eye symptoms in my six cases, all had collateral œdema, and in four it was associated with conjunctival hyperemia; four had tenderness of the globes and pain on rotation; one had subconjunctival ecchymosis; one case showed diplopia as the earliest symptom; one case had acute nephritis, with neuroretinitis and hemorrhages.

Various explanations have been given for the œdema, such as blocking of the lymphatics by the parasites; others, by pressure on the blood-vessels. Bovaird's theory, which seems the most rational, is that the œdema is simply an attendant feature of the myositis and is most noticeable about the eyelids, where serous effusions most readily appear. Microscopic examination of the muscle shows an interstitial myositis, the exudate consisting of small round cells lying in the endomysium and perimysium. A microscopic section of the skin lesion in one of Dr. Bovaird's cases showed engorged subcutaneous capillaries and a serous exudate.

In reporting these cases I have omitted much of the history that might be of interest, and have endeavored to emphasize the eye symptoms as being of especial importance—four of these six patients having sought professional aid on that account. Failure to find the trichinæ in the muscle sections should not mean a negative diagnosis; a case may present the characteristic clinical picture before the trichinæ have developed in sufficient number to be easily discovered.

The important points on which the diagnosis depends are: (1) Muscular pain and tenderness, due to general myositis. (2) Fever resembling that of typhoid. (3) Leucocytosis ranging from ten to twenty thousand. (4) Eosinophilia from 10 to 70 per cent. (5) Œdema of the eyelids, with tenderness of the globe and painful rotation. (6) Finding of the trichinæ, or the inflammatory areas between the muscle fibres.

I have gone more into the general symptoms than my subject would suggest, my purpose being to give briefly the points of diagnostic importance, for I believe that the ophthalmologist is the one most liable to be consulted first by these patients, and I would urge the importance of excluding trichinosis before making a diagnosis of muscular rheumatism, orbital cellulitis, or adenitis of the lacrymal glands.

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XXI.

A CASE OF ADDISON'S DISEASE—DEATH IN COLLAPSE—AUTOPSY.

By Fred. P. Solley, M.D.

F. L., aged twenty-six, born in Belgium, a waiter by occupation, applied for treatment at the Presbyterian Hospital Dispensary on April 12, 1907. His family history was negative. He had had typhoid fever ten years previously. He used alcohol in moderation, tobacco freely.

For one year the skin of his face and hands had been growing darker in color. He had lost fourteen pounds in weight during this time, but was able to work until one month before coming to the Dispensary, when he began to lose strength rapidly. At that time he had a constant feeling of fatigue, and became completely exhausted after the slightest effort. After brushing his hair his arms would drop powerless, and the muscles of his jaw were quickly tired by the act of chewing. He was then obliged to stop work, and went to the country for a rest. There he improved considerably, and was feeling much stronger when he appeared at the Dispensary. He had had occasional attacks of vomiting, but no abdominal discomfort or other evidence of indigestion. From time to time he had been troubled with colds, with some cough, but these never of long duration.

The physical examination at the Dispensary showed brownish pigmentation of the skin, neck, face and forehead, ceasing at the scalp line. The skin of the backs of the hands was still darker in color, deepening over the fingers and especially dark about the nails. The nipples, navel, genitals, and the skin about the anus were deeply pigmented. There was a single very dark patch about one-half inch in diameter in the left gluteal region. On the left forearm was a scar resulting from a burn. The skin about this scar showed pronounced pigmentation, but there was none in the cicatrix itself. The mucous membrane of the inner surface of the lips showed bluish pigmented patches.

There was no enlargement of the area of cardiac dullness. The heart sounds at the apex were feeble and the rhythm was of the fœtal type. The second aortic sound was slightly accentuated. The radial pulse was small and of poor force. The pulse rate 128.

The thorax showed moderate retraction behind the right clavicle, with impaired pulmonary resonance. Over both apices of the lungs the expiratory murmur was prolonged. An occasional creaking râle was heard in both supraclavicular regions, and also in the supraspinous fossæ behind.

The abdomen was negative except for moderate tenderness in the right hypochondrium.

General tonic treatment was prescribed, with powdered suprarenal extract in doses increasing gradually from one to three grains three times a day. Under this treatment the patient's strength improved for a time, and the pulse diminished in frequency from 128 at the first visit to 108 five weeks later. The embryocardia, however, which was noted at the first examination, persisted, and the pulse remained small and of poor force.

There was one attack of vomiting ten days after the first visit, unaccompanied by other digestive disturbance.

After six weeks the patient again began to grow weaker, and suffered from pains in the back. On June 12th, just two months after he first came to the Dispensary, the weakness was so extreme, with a pulse rate of 134, that he was sent to the Hospital wards into the service of Dr. Tuttle.

Through the courtesy of Dr. Tuttle the remainder of the history is taken from the Hospital records.

On admission to the ward the patient was rational, but decidedly apathetic. The temperature was 101° F., the pulse 120 and feeble, and the heart sounds were faint. The physical examination by the house physician revealed nothing of importance in addition to the facts already noted.

On the day after admission the patient passed into a condition of collapse, with vomiting, profuse sweating, cold extremities and very feeble pulse, and he became semi-comatose. The temperature fell to 95° F., and the heart sounds were exceedingly faint. Twenty minims of adrenalin chloride, 1 to 1000, were administered hypodermatically, and hypodermoclysis with twenty minims of adrenalin in normal salt solution, was given. Decided improvement followed for a time, the heart action became stronger and the mind clearer. The next day, however, vomiting again occurred and the temperature rose rapidly to 105° F. The pulse rose to 140 and was very feeble. The patient developed marked restlessness, followed by delirium, during which he several times got out of bed. Finally, the condition of collapse returned, with profuse sweating, shallow respiration, imperceptible pulse, coma, and death on the fourth day after admission.

The examination of the urine showed a trace of albumin, many finely granular casts, considerable indican and a few red blood cells. No reaction for melanin was obtained.

The blood showed hæmoglobin 80%, red blood cells 4,680,000, leucocytes 16,000. The differential leucocyte count showed polymorphonuclears 57%, transitionals 2%, large mononuclears 22%, lymphocytes 17%, basophiles 1%, eosinophiles 1%.

The lesions found at autopsy were as follows:

Heart.—Some minute hemorrhages beneath the pericardium at the base of the left ventricle, near which the muscle shows a definite pale area and softening. Valves normal. Muscle rather pale, a little flabby in places.

Lungs.—The left pleura shows adhesions at the apex. One small area in the lung close to the apex shows beginning softening. About this are groups of recent tubercles. The right lung presents in the upper lobe many minute tubercles and a few small cavities that look like dilated bronchi.

Kidneys.—The left ureter is normal. The kidney capsule free, consistence firm, surface smooth, section congested.

Adrenals.—On section of each adrenal the interior is simply a cheesy mass with foci of softening, of a yellow color.

Intestines.—A small ulcer in the duodenum, just below the pylorus, with some induration around it.

Abnormal Conditions.—Chronic pulmonary tuberculosis, tuberculosis of adrenals, Addison's disease.

XXII.

EXPERIENCES WITH THE CONJUNCTIVAL AND CUTANEOUS TUBERCULIN TESTS AT THE TUBERCULOSIS CLINIC OF THE PRESBYTERIAN HOSPITAL.

By Henry L. Shively, M.D., Physician in Charge of the Tuberculosis Clinic.

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In January of the current year a systematic beginning was made in the examination of all children in the families of tuberculous patients at the Presbyterian Hospital Tuberculosis Clinic. Such action appeared desirable as a result of the visits of the district nurses engaged in the supervision of tuberculous patients in their tenement homes. In many cases the nurse has referred patients to the clinic who had not suspected their disease and it appeared probable that additional cases of tuberculosis would be found where tuberculosis was already known to exist, the opportunity for household infection, especially for children, being most apparent. This view has been further emphasized by the opinion, recently expressed by Holt,[1] that tuberculosis in infants in tuberculous households is far more common than is generally supposed. In nineteen months he has seen sixty-seven cases of pulmonary tuberculosis in infants in whom the diagnosis in over 80 per cent. was made by finding tubercle bacilli in the sputum. Many of these cases presented no symptoms of the disease.

The ordinary methods of diagnosis, satisfactory enough usually in the case of adults, are inadequate when applied to children, the difficulties being much greater in the latter case in reaching

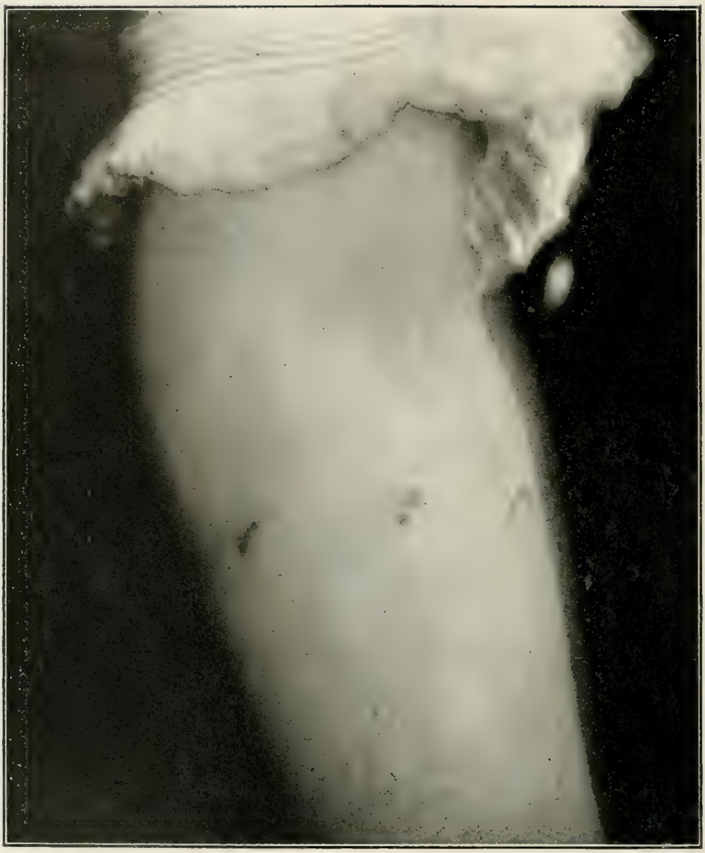

FIG. 1—A NEGATIVE VON PIRQUET REACTION

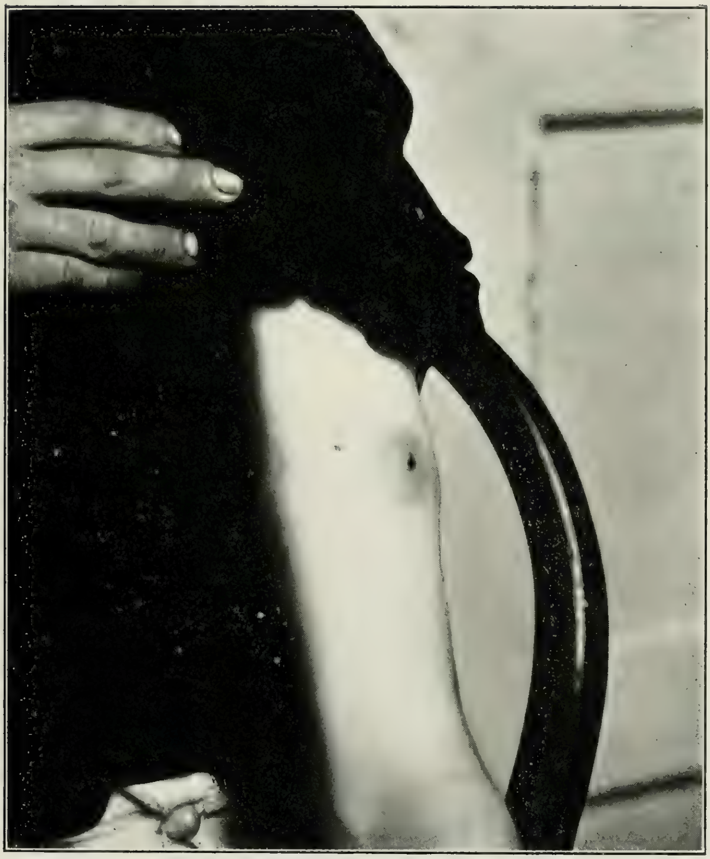

FIG. 2—A WELL-MARKED POSITIVE VON PIRQUET REACTION

a positive conclusion. The physical signs of tuberculosis in young children are ambiguous and often misleading, the temperature and weight records have not the same value as for adults, it is frequently difficult or impossible to obtain sputum for examination, and the injection of tuberculin for diagnostic purposes is unreliable on account of the less stable temperature of children. A certain diagnosis can often only be obtained by careful and long continued observation. It was hoped that in either the Calmette or Von Pirquet test an ideal, rapid, safe and easily applied diagnostic method had been obtained.

Since the publication of Von Pirquet's original communication before the Berliner Medicinische Gesellschaft on May 15, and Calmette's paper before the Académie des Sciences, June 17, 1907, a voluminous literature has arisen regarding the cutaneous and conjunctival tests. Much of this literature is conflicting as to their value, and in many reports there is a disregard evinced for the limitations laid down by Von Pirquet. The positive reaction he considers to be of little value for adults, 90 per cent. of all of whom he distinctly states react positively, owing to latent or healed foci of tuberculosis, which give no clinical symptoms. Between the ages of eight and fourteen, according to Von Pirquet, 35 per cent. of all children, sick and well, react. The test is of greatest value, according to its originator, below the age of two. Von Pirquet claims in his original communication that the only cases of tuberculosis which fail to respond to the test are advanced cases within a week or ten days of death, acute miliary tuberculosis, and cases of tuberculous meningitis.

Calmette considers his conjunctival test to be of greater value than the cutaneous in adults, fewer of whom, without symptoms of tuberculosis, react to the former. He also claims for diagnosis as good results as are obtained from subcutaneous injections of tuberculin, and that, compared with Von Pirquet's test, its results are as good in children and are more reliable for adults.

These claims have been disputed. Klineberger[2] has pointed out that a considerable number of first- and second-stage tuberculous cases with tubercle bacilli in the sputum failed to react to the Calmette test.

Reuschel[3] considers the Von Pirquet test not only distinctly superior to the Calmette, but the most convenient and most suitable of all the tuberculin tests for purposes of diagnosis in the first two years of life, a positive reaction being almost invariably associated with manifest active tuberculosis. After two years, according to him, the negative reaction is of greater value than the positive.

E. Feer[4] also considers the Von Pirquet test to be the more reliable.

Engel and Bauer,[5] however, reported a positive Von Pirquet reaction in five infants in the first year of life with no clinical evidences of tuberculosis. One of these, which came to autopsy, also failed to show, after the most searching pathological examination, any sign of tuberculosis. The other four, when tested, did not react to tuberculin injections.

Sicard and Descomps[6] consider the cutaneous reaction less certain and reliable than the conjunctival test of Calmette.

Olmer and Terras[7] concur in this opinion. French writers in general regard the Calmette as superior, the German prefer the Von Pirquet.

MacLennan,[8] Webster and Kilpatrick[8] also report favorably upon the Calmette test. The latter two writers, in an analysis of one hundred and twenty-one cases, state that all definite cases with bacilli in the sputum reacted positively.

S. Cohn[9] points out that typhoid patients, especially during convalescence, very frequently exhibit a positive reaction to the conjunctival test. He also considers that a second test will often produce a reaction when a negative result was first obtained, that the eye is sensitized by the first instillation, and that the second test is of little value in diagnosing tuberculosis.

Smithies and Walker[10] consider the conjunctival test of undoubted service in the diagnosis of tuberculosis. Out of one hundred and eighty-five patients clinically diagnosed as tuberculous, one hundred and seventy-six gave positive reactions. Out of one hundred and eighty-eight persons suffering from disease not tuberculous, and including a fair proportion of apparently normal individuals, one hundred and eighty-six gave negative reactions, and only two positive.

Joannovics and Kapsammer[11] consider the conjunctival and cutaneous reactions, and also the subcutaneous injection of tuberculin, to be inferior to the method of Bloch, which consists in inoculating guinea-pigs with material supposed to be tuberculous. This he considers to be the best of all the diagnostic tests for tuberculosis.

Weber[12] also considers the subcutaneous injection in the skin of the abdomen of guinea-pigs of supposedly tuberculous material to be the best of all tests for tuberculosis. If the material is tuberculous, lymph-glands in the neighborhood of the injection can be felt at the end of ten to fifteen days, and if these glands are examined the presence of tubercle bacilli within them can be easily demonstrated.

Austin and Grünbaum[13] tried the Calmette test in eight cases of typhoid fever, but failed to obtain a positive result in any. They corroborate the findings of Calmette and French investigators who consider the conjunctival test to be reliable and a useful aid in diagnosis. In twenty-one positive cases they consider twenty were without doubt suffering from tuberculosis.

It was not long after the publication of Calmette's first article advocating the conjunctival test as a routine and harmless method of diagnosis before reports began to appear, especially in Germany, showing that the procedure was not always as devoid of danger as was claimed.

Wiens and Gunther[14] reported a number of cases of conjunctivitis of unusual severity, extreme œdema of the lids, conjunctival hemorrhages, phlyctenulæ, keratitis and pannus following the Calmette test.

Eppenstein[15] has also reported cases of keratitis.

Webster and Kilpatrick[16] report a case of phlyctenular conjunctivitis following the Calmette test.

Barbier[17] reports a case of ulcerative keratitis which resulted in a central leucoma and permanent corneal opacities following the conjunctival test.

Rénon[18] reported a severe case of interstitial keratitis due to the instillation of the 1 per cent. tuberculin solution.

Van Durme and Stocké[19] report five cases of phylctenular conjunctivitis following the Calmette test, and they do not think it is prudent to use the solution stronger than one-half of 1 per cent. for the eye.

Calmette[20] claims that any possible bad eye effects are to be avoided by proper technic, strict asepsis and cleanliness. The conjunctival test he considers[21] is not in itself a source of danger to the eye, but it should be employed only after a thorough examination of the patient's eyes has been made. He considers it safe for diagnosis of disease of the lids and lachrymal ducts, but not for lesions of the eyeball.

Hansell,[22] of Philadelphia, reports a case of double miliary tuberculosis of the conjunctiva in which the Calmette test failed to react. He regards it as of little value. In positive cases of tuberculosis the reaction was present in only 25 per cent.

Last January a supply of precipitated tuberculin in 1 per cent. solution, as recommended by Calmette, was obtained from the Health Department Laboratories, through the courtesy of Dr. William H. Park, for use at the Presbyterian Hospital Clinic, and was employed in the following cases:

Case I. M. S., a girl, aged twelve years. Two brothers have consumption and are under treatment at the clinic. With the exception of whooping-cough and measles, was well until four weeks ago when she began to cough. Muco-purulent, blood-stained sputum, some loss of flesh, short of breath on exertion, appetite and digestion poor, pains in back and chest.

Physical Examination.—May 18, 1907. Pale, poorly nourished. Dullness, bronchovesicular breathing over upper lobes. Temperature, 97; pulse, 98; weight, 78½. January 15. Calmette test positive. May 13. Signs persist. No tubercle bacilli in sputum. Von Pirquet positive.

CASE II. G. G., a girl, aged twelve years. Mother and father have both been treated at the clinic for tuberculosis. Gives a history of cough for an indefinite period; sputum scanty. She has had chilly sensations, fever in the afternoon; appetite poor, is easily fatigued.

Physical Examination.—Pale, poorly nourished child. Dullness, increased breathing over both upper lobes. No tubercle bacilli in sputum; cervical glands enlarged. Temperature, 98.6; weight, 76¾. January 15. Calmette positive.

CASE III. A. G., a boy, aged fourteen years. Sister died of consumption, father has chronic cough. Previous history good except that he has always been delicate. For five weeks he has had a cough, worse at night. Purulent sputum; occasionally hemoptysis and night-sweats; fatigue on exertion, loss of flesh; chilly sensations, fever afternoons. Pains in chest; appetite and digestion poor. Temperature, 98.8; pulse, 90; respiration, 20; weight, 74½.

Physical Examination.—December 11, 1907. Pale, poorly nourished. Dullness, harsh breathing, coarse râles over right upper lobe. February 1. Calmette negative. Cough and physical signs continued for seven weeks and then they began to clear up, râles first disappearing. On March 2, still some dullness and increased breathing over the right upper lobe. On May 1, he had gained 6½ pounds. Temperature was normal and there were no morbid pulmonary signs. In this case a positive clinical diagnosis of tuberculosis was made, which was negatived by the Calmette reaction, and the subsequent clinical course corroborated the findings of the conjunctival test.

CASE IV. M. D., a boy, aged five years. Three sisters have been treated in the clinic for tuberculosis of the lungs; a maternal great-aunt and cousin died of consumption. He had always been a delicate child since an attack of diphtheria at eighteen months, and has had frequent attacks of bronchitis. He was brought for examination. No present symptoms.

Physical Examination.—January 20. Rather undersized and poorly nourished. A few small cervical glands are palpable on left side of neck. Heart and lungs normal. Calmette negative. Temperature, 99.6; pulse, 104; respiration, 24; weight, 39½. May 27. Has recently had a severe attack of measles with complicating broncho-pneumonia, but has developed no signs of tuberculosis. Weight, 40¾.

Case V. E. G., a girl, aged fifteen years. Maternal grandmother and two aunts died of consumption. Had inflammation of the lungs and measles when two years old. For a year and a half she has been delicate. For six months she has had a cough, purulent sputum; hemoptysis a year ago. Loss of flesh and strength, chilly sensations, no fever, marked dyspnœa, no night-sweats, pain in the right chest; appetite variable, digestion fair. Has never menstruated.

Physical Examination.—November 1, 1907. Pale and poorly nourished. The cardiac area is increased downward and to left, apex beat in sixth space; loud presystolic and systolic murmurs at the apex. Pulmonary second sound is much accentuated. Marked dullness, increased breathing and subcrepitant râles over the right upper and middle lobes. Temperature, 98; pulse, 94; respiration, 22; weight, 66½. No tubercle bacilli in sputum. This was rather a puzzling case, resembling others that we have had at the clinic in children in whom, with marked cardiac lesions, there existed signs in the upper part of one or both lungs indicating tuberculosis. December 23. The râles and dullness over the right upper lobe had in great measure cleared up. Temperature, 99.2; weight, 68. By January 6 there was no dullness and the râles had practically disappeared. On January 27, the Calmette test was applied with positive results. The girl's pulmonary symptoms have since entirely cleared up and there is no evidence of tuberculosis.

CASE VI. M. L., a girl, aged twelve years. Well nourished. Brought for examination on account of tuberculosis in the family, the mother being a patient in the clinic. Cough for several months, purulent sputa.

Physical Examination.—January 29. Dullness over left apex anteriorly. Exaggerated breathing and voice at the right apex behind. Calmette reaction negative. June 3. Chills, fever. Cervical glands enlarged. Dullness, increased breathing over left apex, breath-sounds also exaggerated over right apex. Temperature, 99.2; weight, 71½. Von Pirquet positive.

CASE VII. J. M., a boy, aged six years. His father has tuberculosis of the lungs and testicle. Whooping-cough three years ago; measles in February.

Physical Examination.—February 24. Well nourished, healthy looking child. Slight dullness below the second rib over left chest with diminished breathing. Over the right base behind, a few fine crepitant râles. Temperature, 99.4. Calmette reaction positive. May 22. Has had no cough and has good appetite. No morbid pulmonary signs, cervical glands somewhat enlarged. Temperature, 98.6; weight, 39. Von Pirquet positive.

CASE VIII. K. K., a girl, aged fifteen years. Mother under treatment at the clinic for tuberculosis of the lungs. Has had scarlet fever and diphtheria. Was well until a few days ago, when she was attacked by a cough, which has been especially severe at night. Mucopurulent sputum; no hemoptysis. Appetite and digestion good. No loss of flesh or strength.

Physical Examination.—April 24. Pale, poorly nourished. Slight dullness over both apices. Large cervical glands. Temperature, 98; pulse, 90; respiration, 24; weight, 87½. No tubercle bacilli in sputum. Calmette test positive. May 22. Slight dullness over right apex. Temperature, 98.6; weight, 88½. No cough.

Case IX. B. F., a girl, aged thirteen years. Mother and brother have both been under treatment for tuberculosis of the lungs. She was treated in the children's department three years ago for "lung trouble." Has always coughed. Has now purulent sputum; hemoptysis for the first time yesterday; sputum streaked. Has occasional night-sweats, dyspnœa on exertion; chilly sensations, fever afternoons. Has lost flesh and strength and has pain in her left side. Appetite poor, digestion fair.

Physical Examination.—May 15, 1907. Poorly nourished, pale, cervical glands enlarged. Dullness, increased breathing over the right upper lobe. Percussion note high-pitched over left. Temperature, 99; pulse, 92; respiration, 24; weight, 79; a week ago, 83. No tubercle bacilli present in the sputum. After six months, under treatment, signs were slight and doubtful; still had a temperature of 99.2; weight increased to 95½. Calmette test negative. A few weeks later the temperature was normal. No cough or morbid pulmonary signs.

Case X. K. H., aged eighteen years. Stenographer. Family history negative. For a year has had a cough, mucopurulent sputum; occasional hemoptysis and night-sweats. Loss of flesh and strength, fever in the afternoon. Appetite and digestion good. Menstruation scanty and irregular.

Physical Examination.—May 24, 1907. Dullness, increased vocal fremitus, rough breathing over the right upper lobe; cervical glands enlarged. Weight, 110. No tubercle bacilli in sputum. Under treatment her condition improved and her signs became less marked. February 1. Calmette reaction was positive. The patient developed the severest reaction we have seen in the clinic. For more than a week following she had a conjunctivitis and a profuse mucopurulent discharge, her lids being adherent mornings. March 2, weight 113. There was dullness, increased breathing over both apices. Over the right, fremitus increased. Behind, whispering bronchophony. Sputum was again examined on March 11; no tubercle bacilli.

CASE XI. J. T., aged twenty-four years. Carpenter. Family history negative. Typhoid fever, pneumonia, seven years ago. For four months a slight cough, scanty sputum; hemoptysis a month ago. Occasional night-sweats, marked dyspnœa, loss of flesh and strength. Pain in right chest; appetite and digestion fair.

Physical Examination.—March 4. Tall, poorly nourished, ill developed. Dullness, increased breathing over the right upper lobe and left apex. Temperature, 98; pulse, 70; respiration, 22; weight 139½. No tubercle bacilli in sputum. Calmette positive.

An analysis of the Calmette cases, twelve in number, including Case XXVIII of the Von Pirquet series, shows that of seven positive reactions, but three were undoubtedly tuberculous. In three, tuberculosis could be clinically definitely excluded, and one case was doubtful, with the preponderance of evidence in favor of absence of tuberculous disease.

Of the five cases which reacted negatively, three were clinically not tuberculous. In two of these cases a definite positive diagnosis of tuberculosis had been made. In the subsequent course of the disease all symptoms cleared up, physical signs disappeared, and the negative findings of the Calmette test were confirmed. In two cases in which the clinical diagnosis of tuberculosis seemed well established the Calmette was negative.

On account of the severity of the reaction in two cases, one of which resulted in conjunctivitis of considerable intensity, lasting for more than a week, and the appearance in the literature of reports of cases of keratitis, ulceration of the cornea, intense chemosis, pannus and permanent opacities, it was felt that the Calmette test was not as innocuous as had been claimed, and that it was unsuitable to use in the case of strumous and cachectic, poorly nourished children in attendance at a clinic where they could not be kept under constant observation. The Von Pirquet test appeared to be free from these objections, although somewhat less easily applied. A supply of Koch's old tuberculin was obtained from the Health Department which, for use, was diluted to make a 25 per cent. solution with sterile normal salt solution, according to the original Von Pirquet formula.

In each case the arm of the patient was carefully cleansed by scrubbing with green soap, followed by ether and alcohol. The skin was abraded over three small areas of not more than one-fourth inch in extent, separated from each other by a space of an inch, a different sterile needle being used for each case. A small drop of the tuberculin solution was rubbed with the needle point into the two outer abrasions, the inner scarification being used for a control. The surfaces were permitted to dry and the whole concluded by the application of a sterile dressing. The patient was brought to the clinic or visited by the nurse within forty-eight hours after the inoculation.

CASE I. R. S., an Italian girl, aged fourteen years. Family history negative. Except for an attack of measles, has always been well until present illness. Has had a cough for seven months, mostly at night. Purulent sputum. Hemoptysis several months ago. Considerable loss of flesh and strength; occasional night-sweats. Marked dyspnœa. Chilly sensations, fever afternoons; appetite and digestion good. Has menstruated but once, last October.

Physical Examination.—April 24. Pale, poorly nourished. Dullness, bronchial breathing over both upper lobes; below the clavicle near the sternal end at right apex is an area of flatness; cavernous voice and breathing. Over the left upper lobe there are numerous subcrepitant râles. Tubercle bacilli in sputum. Temperature, 99.6; pulse, 140; respiration, 24. Von Pirquet positive.

CASE II. M. F., a girl, aged thirteen years. Mother a patient at clinic with tuberculosis of the lungs. Came for an examination. No pulmonary or other symptoms.

Physical Examination.—April 29. Enlarged cervical glands. Chest shows no morbid signs. Von Pirquet negative.

Case III. J. M., aged eight years. Father died of consumption a year ago. Has tubercular arthritis of the right hip, for which he is wearing a plaster splint applied at the Forty-Second Street Hospital. Had measles and whooping-cough a year and a half ago, since then cough, which has been more severe at night. No sputum. No hemoptysis, dyspnœa on exertion. Loss of flesh and strength; appetite and digestion poor; has fever at night.

Physical Examination.—April 29. Poorly nourished; has enlarged cervical glands; dullness, bronchial breathing, subcrepitant râles over both upper lobes, more marked over right. Temperature, 98.6; pulse, 96; respiration, 24; weight, 45½. Von Pirquet test positive.

Case IV. J. T., aged eight years. For four weeks has had a cough and mucopurulent sputum.

Physical Examination.—January 27. Pale. Cervical glands enlarged. Heart and lungs normal. April 1. Had measles. Cough since then. Profuse night-sweats; has lost flesh; fever at night; appetite poor; no positive pulmonary morbid signs. Cervical glands much enlarged. Temperature, 98; weight, 49⅞. Von Pirquet positive. June 5. Moderate dullness, fine râles over right upper lobe. Temperature, 98.4; weight, 51¼. No tubercle bacilli in sputum.

Case V. J. M., a girl, aged seventeen years. Mother died of consumption, also two maternal aunts and an uncle, and another maternal uncle is tuberculous. She has had measles, and seven years ago typhoid fever. Is under treatment for atrophic rhinitis. Has had a winter cough for several years. Cough is worse mornings; sputum is purulent, has several times been streaked with blood. She has lost flesh and strength; has profuse night-sweats, marked dyspnœa on exertion, occasional chills, pain in chest, fever afternoons; appetite poor, digestion good. Amenorrhea for two months.

Physical Examination.—May 1. Pale, ill nourished, stoop shouldered. Dullness over both upper lobes, breathing sounds rather diminished. Temperature, 99.4; pulse, 100; respiration 22; weight, 103⅛. No tubercle bacilli in sputum. Von Pirquet negative. June 5. Signs persist. Temperature, 100; weight, 104⅛.

Case VI. G. B., aged thirty-eight years. Insurance solicitor. Family history negative as to tuberculosis. He had "inflammation of the lungs" when two years old; pneumonia seven years ago. Was rejected for life insurance four years ago by several companies. At that time his physician found a low percentage of sugar in the urine. For three years he has had a slight morning cough with purulent sputum, and for the past year has failed in strength and has lost weight. No hemoptysis or night-sweats; occasional chilly sensations and fever. Appetite and digestion good.

Physical Examination.—April 15. Well nourished, not anæmic. Slight dullness and increased breathing over the right apex. Temperature, 98; pulse, 72; respiration, 24; weight, 164. No glucose in urine. No tubercle bacilli in sputum. Von Pirquet positive. May 18. Signs persist at right apex. Temperature, 99.5; weight, 163¾.

Case VII. W. O., a boy, aged sixteen years. Mother died of consumption. He has had measles, scarlet fever and for four years has had a slight cough. Mucopurulent sputum, frequent night-sweats. Occasional chills, and fever in the afternoon. Appetite and digestion fair.

Physical Examination.—April 27. He is undersized, pale, poorly nourished. Dullness, increased breathing and whisper over both upper lobes. Temperature, 99; pulse, 96; respiration, 22; weight, 68¼. May 4. Von Pirquet negative. May 22. Signs are less marked. Dullness, bronchial breathing persists over right upper lobe. Temperature, 98.6; weight, 69½.

Case VIII. M. K., a baker, aged twenty-seven. No morbid family history. No previous illness. He caught cold one month ago. Since then a cough, purulent sputum, night-sweats, loss of flesh, some shortness of breath; no hemoptysis; appetite and digestion poor.

Physical Examination.—May 4. Fairly well nourished. Percussion note is high-pitched, increased tactile fremitus over the right upper lobe and left apex. A few clicks on coughing are heard posteriorly over each upper lobe, more over the left than right. Temperature, 98.6; pulse, 76; respiration, 22; weight, 155½. No tubercle bacilli in sputum. Von Pirquet positive.

Case IX. W. C., aged thirty-two years. Bartender. Excessive alcohol habit. Family history negative. Had croup when seven years old. Hemoptysis two years ago. Has otherwise been well until three months ago, when he began to cough. Purulent sputum. Dyspnœa on exertion; loss of flesh and strength, occasional chills, fever in afternoons; pain in chest; appetite good, digestion fair. Marked dysphonia.

Physical Examination.—April 29. Emaciated, hectic, dullness, increased vocal fremitus, bronchial breathing and whisper over both upper lobes; over right, subcrepitant râles. Temperature, 101; pulse, 100; respiration, 22; weight, 114; a few months ago, 120. Laryngological examination shows infiltration of arytenoids and interarytenoid commissure. Many tubercle bacilli in sputum. Von Pirquet positive.

Case X. M. S., a girl, aged sixteen years. Father died a year ago of consumption. She was in good health until four months ago when she began to cough. Purulent sputum, night-sweats, loss of flesh and strength, dyspnœa, fever afternoons. No hemoptysis. Appetite poor. Amenorrhea for two months.

Physical Examination.—February 21. Marked dullness, bronchial breathing. Increased whisper over right upper lobe; over left apex there is flatness, diminished breathing, cavernous whisper, numerous subcrepitant râles. Temperature, 100; pulse, 104; respiration, 24; weight, 102. Tubercle bacilli present in large numbers in sputum. May 6. Temperature, 102.2; weight, 101¼. Von Pirquet negative. May 25. Signs persist. Temperature, 101.4; weight, 100½.

CASE XI. R. B., a girl, aged twelve years. Half sister has tuberculous arthritis of the hip. She was in good health until two months ago, when she began to cough. Had severe paroxysms of coughing at night; sputum purulent. Hemoptysis for the first time to-day. Has had night-sweats for a week. Shortness of breath, loss of flesh and strength, frequent chills and fever at night. Appetite poor, digestion fair.

Physical Examination.—May 6. Pale and sallow; fairly well nourished. Numerous enlarged cervical glands. Moderate dullness over both apices. Temperature, 98.6; pulse, 86; respiration, 20; weight, 93½. No tubercle bacilli in sputum. Von Pirquet positive.

CASE XII. M. D., a girl, aged twenty years. Telephone operator. Maternal grandmother died of tuberculosis, an uncle died of tuberculous laryngitis and a maternal aunt has been treated for tuberculosis of the lungs at the clinic. With the exception of measles and whooping-cough, has been well until an attack of lobar pneumonia a month ago, complicated with median otitis of both ears. Has had cough since her attack of pneumonia; sputum is purulent. No hemoptysis or night-sweats; no fever. Appetite is poor, but digestion good. Menstruation is regular.

Physical Examination.—May 1. Pale, but fairly well nourished; slight dullness, perhaps, over the right upper lobe, is the only suspicious sign in chest. Temperature, 98.6; pulse, 76; respiration, 20; weight, 109½, was 115 recently. No tubercle bacilli in sputum. Von Pirquet is negative. June 5. No pulmonary symptoms.

CASE XIII. T. U., a girl, aged nineteen years. Waitress. A cousin died of consumption. Father has a chronic cough. She was treated for cough eight years ago, and four and a half years ago she had ulcers of the leg, which were five months in healing. She has had a slight cough for six months. Purulent sputum, no hemoptysis; had night-sweats last summer. Slight loss of flesh, occasional chills, fever in the afternoon. Appetite and digestion good. Menstruation regular.

Physical Examination.—March 13. Well nourished, somewhat flushed. Numerous enlarged cervical glands, those at the base of the right side of the neck being tender and painful. There are dullness, bronchovesicular breathing, and subcrepitant râles over both upper lobes, behind; over the right, the whispered voice is increased. Temperature, 99.8; pulse, 90; respiration, 22; weight, 133. Many tubercle bacilli in sputum. May 4. Von Pirquet positive.

CASE XIV. A. P., Italian girl, aged sixteen years. Family history as to tuberculosis negative. She was well until a month ago, since which time she has had a cough, which is worse mornings. Purulent sputa, loss of flesh and strength, frequent night-sweats. Occasional chills, fever afternoons. Dyspnœa on exertion; no hemoptysis. Pain in her left chest; appetite and digestion fair. Menstruation regular.

Physical Examination.—April 29. Pale, sallow, poorly nourished. Dullness, bronchial breathing and whisper; subcrepitant râles over upper two-thirds of the entire pulmonary area. Temperature, 99.2; pulse, 106; respiration, 22; weight, 83¾. No tubercle bacilli in sputum. May 11. Von Pirquet negative.

CASE XV. N. G., a girl, aged twenty years. Sister has been treated at the clinic for tuberculosis of the lungs. She had diphtheria at the age of six. Is very nervous. For seven weeks she has had cough, worse mornings. Purulent sputum, loss of flesh and strength, chilly sensations, fever in the afternoon. No hemoptysis. Pain in the right shoulder; appetite poor, digestion good. Menstruation regular.

Physical Examination.—March 27. She is pale, but fairly well nourished. Slight dullness over the right apex, behind the breathing and whisper are increased and fine râles are heard. Temperature, 99.4; pulse, 100; respiration, 24; weight, 106. No tubercle bacilli in sputum. May 11. Von Pirquet positive. June 5. No râles. Moderate dullness, increased breathing over right apex. Temperature, 99; weight, 105⅛. Very pale.

Case XVI. M. B., a girl, aged seventeen years. Mother is under treatment at the clinic for pulmonary and laryngeal tuberculosis. Had scarlet fever and diphtheria at the age of two and one-half years. For two months she has had a slight cough. Purulent sputum, no hemoptysis, profuse night-sweats, loss of flesh and strength, fever afternoons; appetite and digestion good. Menstruation regular.

Physical Examination.—May 15. Cervical glands are a little enlarged. No morbid pulmonary signs. No tubercle bacilli in sputum. Von Pirquet positive.

Case XVII. J. W., a boy, aged seventeen years. Both parents died of consumption. Diphtheria six years ago. Has had for many years enlarged glands in the neck. For two months has had a slight cough, mucopurulent sputum. One night-sweat recently. No loss of flesh or strength, some dyspnœa. Fever afternoons. Appetite fair, digestion good.

Physical Examination.—May 6. Poorly nourished, pale, undersized boy. Dullness, increased breathing, fine râles over the right upper lobe. Over the left apex percussion note is high-pitched; breathing is increased. Temperature, 100.8; pulse, 104; respiration, 22; weight, 77¾. Numerous enlarged glands on both sides of neck from the size of a bean to a good-sized nut. No tubercle bacilli in sputum. Von Pirquet positive.

Case XVIII. S. P., a girl, aged seventeen years. Grandfather and two aunts died of consumption. Measles at the age of four. Otherwise well until three months ago, when she began to cough. Sputum purulent. Has had night-sweats for two months; loss of flesh and strength; fever at night; appetite poor, digestion fair. Menstruation regular.

Physical Examination.—April 3. Poorly nourished, pale. Dullness, increased breathing and whisper over both upper lobes. Temperature, 98.8; pulse, 88; respiration, 20; weight, 96. Tubercle bacilli present in sputum. May 1. Fine râles over the right apex. Other signs continue same. Temperature, 100.2; May 8. Von Pirquet positive.

Case XIX. E. A., a girl, aged fourteen years. An uncle and an aunt died of consumption. An uncle is now under treatment for tuberculosis of the lungs at this clinic. Patient had measles seven years ago, and "malaria" symptoms for the past year. She has had a slight cough for six weeks. Mucopurulent sputum. Loss of flesh and strength; fever afternoons. Dyspnœa on exertion; frequent chilly feelings. Appetite poor. Vomits frequently mornings. Has never menstruated.

Physical Examination.—March 23. She is fairly nourished, but undersized. Dullness, increased tactile fremitus, bronchovesicular breathing, increased whisper over the right upper lobe; behind there are coarse râles over the right apex. Temperature, 100.2; pulse, 122; respiration, 24; weight, 74½. No tubercle bacilli in sputum. On April 22, moderate dullness and increased breathing are detected over the left apex also. Temperature, 99; weight increased to 77¼. Von Pirquet positive.

Case XX. J. V., a girl, aged thirteen years. Sister is under treatment for tuberculosis of the lungs at the clinic. She comes for examination. Has no cough or other symptoms.

Physical Examination.—May 8. Patient is rather anæmic, undersized. Has no enlarged glands. Heart and lungs appear normal. Temperature, 98; weight, 65. Von Pirquet positive.

Case XXI. W. P., a girl, aged eleven years. Mother is being treated for consumption at the clinic. Has had measles and whooping-cough during infancy. Has had a cough for three days; no sputum.

Physical Examination.—May 11. Poorly nourished, pale. Dullness over both upper lobes, cervical glands slightly enlarged. Temperature, 99.2; weight, 72. Von Pirquet positive. May 13. Temperature, 99.2. June 3. Subcrepitant râles over left upper lobe behind; over right, breathing is increased behind. Temperature, 98.6; weight, 70⅞.

Case XXII. A. Z., aged eight years. Father is being treated for tuberculosis of the lungs. He was brought for examination, *Physical Examination.*—March 25. Rather undersized, pale and slight. Heart and lungs at that time negative. On May 11, cervical glands enlarged. Dullness over both upper lobes. Temperature, 99.8; weight, 45. Von Pirquet positive. May 13. Dullness over both upper lobes. Temperature, 99.6.

CASE XXIII. C. B., a girl, aged sixteen years. Worker in paper boxes. Mother has pulmonary and laryngeal tuberculosis, a sister and brother are suspects. Previous health good and has no symptoms.

Physical Examination.—May 18. No morbid pulmonary signs. Temperature, 99.4; pulse, 84; respiration, 22; weight, 99¾. Von Pirquet negative. This patient has since become positively tuberculous and has spent several months at Stony Wold Sanatorium.

CASE XXIV. E. W., a girl, aged sixteen years. A sister is under treatment at the clinic for tuberculosis of the lungs. She had pneumonia at the age of seven and again at ten. Health good until the age of twelve, when she was operated on for tuberculous glands of the neck at the Presbyterian Hospital. She began to cough in February of this year. Has had mucopurulent sputum, which has several times been streaked with blood. She has had night-sweats for the past month; short of breath on exertion; has lost flesh and strength; fever afternoons; appetite and digestion poor. Has had amenorrhea for five months.

Physical Examination.—April 29. Marked dullness over both lungs anteriorly and posteriorly apex to base; flatness, cavernous voice and breathing, showing the presence of large cavities in the upper lobes of both lungs; numerous moist, sticky râles. Temperature, 100.4; pulse, 120; respiration, 22; weight, 113. Many tubercle bacilli present in sputum. May 22. Temperature, 99.6; weight had decreased to 109¼. Von Pirquet positive.

CASE XXV. M. B., aged nineteen years. Shop girl. Mother has had chronic lung trouble. She had scarlet fever when three years old, also measles. Four weeks ago had adenoids removed. Has had a slight cough for a year. Mucopurulent sputum, night-sweats for a month. Dyspnœa on exertion; loss of flesh and strength; chilly sensations; fever afternoons; pain in the right shoulder; appetite poor, digestion good. Menstruation scanty.

Physical Examination.—March 25. Cervical glands are much enlarged, especially on the left side of the neck. Dullness, slightly increased breathing over both upper lobes. Temperature, 100.4; pulse, 126; respiration, 24; weight, 115; a year ago, 130. No tubercle bacilli in sputum. May 11. Her glands are considerably diminished in size and pulmonary signs are less marked. Temperature, 99.2; weight, 120. Von Pirquet is positive. Reaction extensive, with a well-marked vesicular eruption.

CASE XXVI. M. B., a girl, aged eighteen years. Cashier. No morbid pulmonary history in family. She had pneumonia, diphtheria and scarlet fever as a child. No cough. Two months ago slipped and fell, injuring her left knee, following which she has had synovitis and considerable effusion in the joint.

Physical Examination.—May 22. Heart and lungs negative. The left knee is moderately swollen. No heat or redness. Temperature, 98.2; weight, 114½. Von Pirquet positive. June 1. Knee is much improved.

CASE XXVII. E. A., a girl, aged eleven years. Family history negative. She had diphtheria when three years old, measles at five, scarlet fever, whooping-cough and chicken-pox two years ago. For six weeks she has had a slight cough, purulent sputum, no night-sweats or hemorrhages, no dyspnœa, a little fever in the afternoon, no loss of flesh; appetite good, digestion fair.

Physical Examination.—May 22. Fairly nourished, a little flushed; has enlarged cervical glands, dullness, bronchovesicular breathing, coarse and creaking râles over the right apex. Temperature, 99.2; pulse, 112; respiration, 24; weight, 66. No tubercle bacilli in sputum. Von Pirquet positive.

CASE XXVIII. J. H., a married woman, aged seventeen years. Family history negative. She was treated in the Presbyterian Hospital two months ago for a dry pleurisy. At that time, besides her cough, she had occasional hemoptysis. There were no tubercle bacilli in the sputum, and the conjunctival tuberculin test was negative. She was discharged on March 11. On May 20, she came to the clinic with a history of cough of four months' duration. Purulent sputum, some dyspnœa on exertion, loss of flesh and strength, a little fever in the afternoon, pain in the back and chest.

Physical Examination.—May 20. Pale, but well nourished. Slight dullness, increased tactile fremitus over right apex; behind the breathing is increased. Temperature, 99.8; pulse, 100; respiration, 22; weight, 121½. No tubercle bacilli in sputum. Von Pirquet negative. May 22. Temperature. 100.2. June 5. Dullness, increased breathing and whisper over right apex. Temperature, 101.4; weight, 118⅞. A considerable hemoptysis to-day. Pain and tenderness in right groin. Vaginal examination shows to right of uterus a tender, painful, obscurely fluctuant mass size of a lemon. June 10. Operation for double pyosalpinx.

CASE XXIX. A. L., a boy, aged eleven years. Mother is under treatment at the clinic for tuberculosis of the lungs. January 29, he came for examination. Heart and lungs negative. Enlarged cervical glands. No cough or other pulmonary signs. May 22. Von Pirquet negative.

CASE XXX. R. S., a girl, aged eighteen years. Family history negative. Cough, mucopurulent sputum; hemoptysis for two months. Loss of flesh and strength; occasional chills, fever afternoons; dyspnœa on exertion; night-sweats, pain in right side; appetite and digestion poor. Menstruation regular.

Physical Examination.—March 2, 1908. Fairly well nourished, pale. Dullness, fine râles over right apex. Temperature, 98.6; pulse, 96; weight, 124¾. No tubercle bacilli in sputum. Von Pirquet positive.

CASE XXXI. C. C., a girl, aged fifteen years. Father died of pneumonia; family history otherwise negative. She had typhoid fever when nine years old. Was at Raybrook for six months one year ago. Has had cough for a year and a half. Purulent sputum, occasionally streaked with blood; loss of flesh and strength, marked dyspnœa; fever afternoons; frequent chills; pain in the right chest; appetite good, digestion poor. Amenorrhea for two months.

Physical Examination.—March 9. Fairly nourished. Numerous enlarged cervical glands. Dullness, increased breathing and whisper; fine subcrepitant râles over both upper lobes, more marked over the right. Temperature, 100.4; pulse, 120; respiration, 24; weight, 95½. Tubercle bacilli present in large number in sputum. May 13. Signs persist. Temperature, 100.6; weight, 93. Von Pirquet positive, but slight reaction.

CASE XXXII. A. W., a girl, aged twenty years. Cigarette maker. Father said to have died of consumption. Diphtheria at the age of five. Rheumatism nine months ago. Cough for two months; purulent sputum. No hemoptysis; loss of flesh and strength. Pain in the chest; appetite and digestion poor. Menstruation regular.

Physical Examination.—May 18. Emaciated, chest retracted below clavicles, especially right. Dullness, increased fremitus, bronchial breathing and whisper at the left apex. Dullness, increased whisper over right upper lobe. Temperature, 100.6; pulse, 92; respiration, 20; weight, 96.¾. Von Pirquet positive.

CASE XXXIII. F. B., a boy, aged eleven years. Mother under treatment for laryngeal and pulmonary tuberculosis; has had a cough for an indefinite period.

Physical Examination.—Pale, poorly nourished, left chest is retracted below the clavicle, slight dullness over both upper lobes, no râles, cervical glands are enlarged. Temperature, 98.6; pulse, 90; respiration, 22; weight, 61½. Von Pirquet negative.

CASE XXXIV. L. S., a married woman, aged twenty-eight years. Four uncles and aunts have died of consumption. Has always been well until one year ago when she began to cough. Has had scanty purulent sputum, loss of flesh and strength, marked dyspnœa, no chills, no fever; appetite fair, digestion poor. Four months pregnant.

Physical Examination.—April 17. Emaciated, pale. Dullness, bronchial breathing, increased whisper over nearly the whole pulmonary area. Temperature, 98; pulse, 80; respiration, 20; weight, 124. A few tubercle bacilli present in sputum. May 18. Slight hemoptysis for first time. May 27. Von Pirquet positive, but slight.

CASE XXXV. L. M., a girl, aged nineteen years. Cigarette packer. No tuberculous family history. A year ago had a hemorrhage from the lungs. Since then cough, purulent sputum, occasionally feverish, pain in the right chest, no dyspnœa or nightsweats; appetite good, digestion poor. Menstruation regular.

Physical Examination.—February 10. Dullness over both upper lobes, lower over the right; râles anteriorly and posteriorly, increased tactile fremitus. Temperature, 99.6; pulse, 86; respiration, 24; weight, 95. Tubercle bacilli present in sputum. May 8. Weight, 91½. May 22. Attacks of hemoptysis coincide with her menstrual periods. Von Pirquet positive.

CASE XXXVI. J. M., a girl, aged three years. Father under treatment for pulmonary tuberculosis. Measles a year ago. Has been subject to cough, which for the last week has been severe; purulent sputum.

Physical Examination.—May 29. Well nourished, no anæmia. Cervical glands somewhat enlarged. Breathing harsh over both upper lobes. Temperature, 99.4; weight, 31½. Von Pirquet negative. June 1. Cough much better; breathing sounds normal. Temperature, 99.

CASE XXXVII. M. V., a girl, aged seventeen years. Cigarette maker. Father died of consumption in the Seton Hospital. She was well until two years ago when she began to cough. Has never had any expectoration. No night-sweats, no loss of flesh, some dyspnœa on exertion. Appetite and digestion fair. Pain in the left chest. Menstruation regular. She was in the Seton Hospital two and one-half months. Came out one month ago.

Physical Examination.—March 27. Slight dullness, increased breathing over the right apex, whisper increased posteriorly. Temperature, 98.8; pulse, 88; respiration, 20; weight, 110. May 27. Signs are very slight. Temperature, 98.6; weight, 105. Never has any sputum, unable to examine for tubercle bacilli. Von Pirquet positive.

CASE XXXVIII. M. S., a girl, aged eighteen years. Cashier. Father has tuberculosis of the lungs and tuberculous arthritis of the right shoulder. Mother died of consumption. Was operated on for appendicitis four years ago Pleurisy and pneumonia three years ago, since which time she has had a slight cough at times; no sputum. Dyspnœa on exertion; chilly sensations; loss of flesh and strength; pain at times in right shoulder. No fever, hemoptysis or night-sweats. Appetite fair and digestion good. Amenorrhea for three months.

Physical Examination.—June 3. Pale, poorly nourished, numerous râles over the left upper lobe, front and back. Percussion note and breathing little altered. Several cervical glands enlarged. Temperature, 98.6; pulse, 124; respiration, 22; weight, 101¾. Von Pirquet negative. June 6. Râles had disappeared. June 10. Well-marked dullness over right upper lobe.

Of the Von Pirquet tests, forty-one in number, including cases I, VI and VII of the Calmette series, twenty-nine reacted positively. In twenty a definite clinical diagnosis of tuberculosis of the lungs was made. Of four doubtful cases, in three the weight of clinical evidence would incline to a diagnosi of tuberculosis. In the twelve negative Von Pirquet reactions, in six tuberculosis of the lungs was definitely present and satisfactorily established by all the clinical signs and symptoms, in one case tubercle bacilli being present in the sputum. In five tuberculosis was not present and one case was doubtful. In four cases both the Calmette and Von Pirquet tests were tried. In two of these both were positive, in one both were negative, and in one case they conflicted, the Calmette being negative, the Von Pirquet positive, the clinical diagnosis corresponding with the latter.

In the majority of cases here reported the patients have been under careful observation for a period of several months and, it is believed, have been studied with sufficient care to establish or exclude a diagnosis of tuberculosis as far as this is possible from clinical observation alone. It would seem that in the employment of these tests there are sources of error which cannot be satisfactorily explained, and which are frequent enough to cause little dependence to be placed upon them in doubtful cases. If, as Calmette claims, these newer methods are as certain and reliable as tuberculin injections for diagnostic purposes, it would appear that none of the tuberculin tests is absolutely to be trusted. It is probable that in the majority of older children and adults the test is one of too great delicacy, unimportant, healed and latent foci producing a reaction in an apparently healthy individual as intense as manifest tuberculosis with active symptoms. It is more difficult to account for the first and second stage cases, sometimes with bacilli in the sputum, which fail to react. A number of these cases at the clinic have been in fair general condition and cannot be accounted for by Von Pirquet's exceptions in the last stages of tuberculous disease. It would perhaps be unwarranted to draw any general conclusions as to the value of these tests from the number of cases here studied, but as far as they go, it would appear that both the conjunctival and cutaneous tests would very frequently be misleading if depended upon for the diagnosis of doubtful cases of tuberculosis.

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XXIII.

THE OPHTHALMIC REACTION IN THE DIAGNOSIS OF TUBERCULOUS CONDITIONS.

WITH SPECIAL REFERENCE TO THE LUNGS AND SKIN.

By Henry Hubbard Pelton, A.M., M.D., Chief of the Medical Clinic.

(*Reprinted from the New York Medical Journal for June* 27, 1908.)

Since Calmette's original papers[1] the ophthalmic reaction to tuberculin has become too familiar to the profession to need full description here. It is sufficient to state that, with certain exceptions, when a small amount of sterilized one-half to one per cent. solution of dry tuberculin in normal saline solution is instilled into the conjunctiva of a patient who is the subject of tuberculous disease, a local reaction takes place. In most instances where this positive reaction is obtained within three to forty-eight hours after the instillation, the semilunar fold and caruncle become reddened and the conjunctiva becomes congested, the general appearance being that of an acute infectious conjunctivitis. The reaction reaches its height in from six to ten hours, and, as a rule, disappears in from eighteen to thirty-six hours. There may be slight lachrymation and the eyelids may be gummed together when the patient awakes in the morning, but the discomfort is very slight. The positive reaction varies in degree from a moderate congestion of the caruncle and conjunctiva to marked œdema of these structures with fibrinopurulent secretion and photophobia. The local reaction is apparently accompanied by no constitutional disturbance nor is the local tuberculous process influenced in any degree. Diseases of the eye contraindicate the employment of the test. For a more detailed description of the types in which the reaction may manifest itself the reader is referred to the paper of Smithies and Walker.[2]

A number of instances in which untoward results have followed the use of the test have been reported. These have varied from persistent conjunctivitis[3] to interstitial keratitis;[4] one instance of destruction of the eye has also been reported.[5] In the writer's cases there were but two instances of marked conjunctivitis (cases XX and XXIII); these persisted for from ten days to two weeks; one case of persistent phlyctenular conjunctivitis has been observed in a patient who underwent the test in the wards of the Presbyterian Hospital.

In most of the patients reported in this paper a one per cent. solution of tuberculin was used, but in a few a solution of one-half per cent. strength was employed. The amount instilled in each instance was 0.025 c.c., which was measured in a graduated throttle pipette, this instrument being sterilized by boiling before use. The technique employed in the instillations was that described by Baldwin.[6]

It has been stated that the tuberculin solutions are not stable, but the one per cent. solution used by the writer remained potent for at least two months. When not in use it was kept tightly corked at an ordinary temperature. The tuberculin employed was furnished to the Presbyterian Hospital by the Rockefeller Institute of New York city.

When this study was undertaken it was intended to embrace only patients suffering from or suspected of being subjects of pulmonary tuberculosis, but owing to the kindness and interest of Dr. Jerome Kingsbury, class head in dermatology at the Presbyterian Hospital, Out Patient Department, a number of dermatological cases became available, and the results obtained in these are incorporated in this report. Most of the patients tested were selected from those applying for treatment at the Presbyterian Hospital, Out Patient Department, but two are from the writer's private practice, and several of the dermatological cases are from the service of Dr. Kingsbury at the New York Skin and Cancer Hospital. In recording the results obtained the following scheme[7], which is practically that of Baldwin, has been adopted: o, No difference in either conjunctiva. ?, Slight difference, especially in caruncle. +, Distinct redness of caruncle and palpebral conjunctiva. + +, Distinct redness of palpebral and bulbar conjunctiva with lachrymation and formation of fibrin. + + +, Œdema of lids and photophobia (chemosis).

CASE I. L. B., female, aged fourteen years. Clinical diagnosis: Pulmonary tuberculosis (second stage). Bacilli found in sputum. January 31, 1908, one-half per cent. tuberculin in right eye. Result, + +.

CASE II. A. H., female, aged thirty-six years. Clinical diagnosis: Probable pulmonary tuberculosis, incipient. No bacilli found in sputum. In this patient the physical signs were hardly sufficient to assure the diagnosis, and it is in such cases, in the writer's opinion, that the ophthalmic test will find its greatest field of use in the diagnosis of pulmonary tuberculosis. April 1, 1908, one per cent. tuberculin in right eye. Result, O. April 13, 1908, one per cent. tuberculin in left eye. Result, +.

CASE III. E. R., female, aged twenty-two years. Clinical diagnosis: Pulmonary tuberculosis, first stage. No bacilli found in sputum. January 31, 1908, one-half per cent. tuberculin in right eye. Result, O. March 27, 1908, one per cent. tuberculin in right eye. Result, +.

CASE IV. B. F., female, aged thirty years. Clinical diagnosis: Pulmonary tuberculosis, second stage. Bacilli found in sputum. February 7, 1908, one-half per cent. tuberculin in right eye. Result, +.

CASE V. F. McP., male, aged sixty years. Clinical diagnosis: Pulmonary tuberculosis, third stage. Bacilli found in sputum. April 10, 1908, one per cent. tuberculin in right eye. Result, +.

CASE VI. L. U., male, aged forty years. Clinical diagnosis: Pulmonary tuberculosis, third stage. Potts' Disease. No bacilli found in sputum. March 11, 1908, one per cent. tuberculin in right eye. Result, O. March 25, 1908, one per cent. tuberculin in right eye. Result, +.

CASE VII. J. F., male, aged forty-one years. Clinical diagnosis: Pulmonary tuberculosis, second stage. Bacilli found in sputum. March 29, 1908, one per cent. tuberculin in right eye. Result, +.

CASE VIII. G. H., male, aged thirty-four years. Clinical diagnosis: Pulmonary tuberculosis, quiescent. This patient applied at the dispensary some two years ago in the second stage of the disease; bacilli were present in his sputum. He has done well under treatment and has gained twenty pounds. The signs of his old lesion are still demonstrable. February 10, 1908, one-half per cent. tuberculin in right eye. Result, + +.

CASE IX. J. R., male, aged forty-four years. Clinical diagnosis: Pulmonary tuberculosis. The history of this patient is very similar to that of Case VIII.

Bacilli were formerly present in his sputum, but have now disappeared. March 20, 1908, one per cent. tuberculin in right eye. Result, O. April 10, 1908, one per cent. tuberculin in right eye. Result, +.

Case X. C. J., female, aged twenty years. Clinical diagnosis: Pulmonary tuberculosis, incipient. This patient has been under the writer's care at intervals for about four years. During the summer of 1907 she underwent an attack of pleurisy with serous effusion; this was treated by means of thoracocentesis. Recovery took place, but the clinical symptoms since her pleurisy led to the belief that there was a tuberculous lesion in the lungs, although no very definite signs could be demonstrated, nor were tubercle bacilli found in the sputum. It is in such patients that the ophthalmic test will prove extremely useful if further experience shows that it is reliable. March 7, 1908, one per cent. tuberculin in right eye. Result, +.

Case XI. M. O'B., male. Clinical diagnosis: Bronchiectasis; pulmonary tuberculosis, third stage. Bacilli found in sputum. February 7, 1908, one-half per cent. tuberculin in right eye. Result, O. Feburary 18, 1908, one per cent. tuberculin in right eye. Result, O. March 14, 1908, one per cent. tuberculin in left eye. Result, O. April 4, 1908, one per cent. tuberculin in right eye. Result, +.

Case XII. M. L. M., female, aged forty-one years. Clinical diagnosis: Pulmonary tuberculosis, first stage. Surgical kidney. March 5, 1908, one per cent. tuberculin in right eye. Reaction, +. This patient was referred to the writer by Dr. George B. Campbell. Her family history was tuberculous, and she had been suffering from a bladder disorder for twelve years. The urine contained pus, and three times during the past three years a tumor appeared just above the left groin. Each time the tumor disappeared suddenly, without, however, any associated sudden increase in the flow of urine. Physical examination revealed the presence of a small tuberculous infiltration in the right lung, and of two palpable kidneys, the left larger than the right and tender. A diagnosis of pulmonary tuberculosis and left pyonephrosis, possibly tuberculous, was made. No tubercle bacilli were found in the urine. The patient was sent to the Presbyterian Hospital, where the diagnosis of surgical kidney was confirmed by cystoscopy and ureteral catheterization, the pus from the affected kidney containing *Bacilli coli* in pure culture. Subsequently nephrectomy was performed by Dr. Ellsworth Eliot, Jr. The patient made an uneventful recovery.

Case XIII. J. C., male, aged twenty-five years. Clinical diagnosis: Cerebral syphilis (?); tuberculous brain lesion (?). February 24, 1908, one per cent. tuberculin in right eye. Reaction, O. This patient was seen at the Manhattan Eye and Ear Hospital by the courtesy of Dr. Frank J. Parker. The facts that the symptoms rapidly disappeared under the administration of potassium iodide in large doses, and that the ophthalmic reaction was negative, would seem to rule out tuberculosis as a factor in the condition.

Case XIV. Female, aged twenty years. Clinical diagnosis: Probable incipient pulmonary tuberculosis. February 17, 1908, one per cent. tuberculin in right eye. Reaction, O. April 21, 1908, one per cent. tuberculin in left eye. Reaction, O.

Case XV. D. L., female, aged sixteen years. Clinical diagnosis (chiefly on history): Possible incipient pulmonary tuberculosis. No bacilli found in sputum. February 14, 1908, one per cent. tuberculin in right eye. Reaction, O. May 1, 1908, one per cent. tuberculin in left eye. Reaction, O.

CASE XVI. C. K., male, aged thirty-seven years. (Control test). Clinical diagnosis: Alcoholic gastritis. March 16, 1908, one per cent. tuberculin in right eye. Reaction, O. April 21, 1908, one per cent. tuberculin in left eye. Reaction, O.

CASE XVII. W. N., male, aged thirty-seven years. (Control test). Clinical diagnosis: Anæmia; possible carcinoma of stomach. March 9, 1908, one per cent. tuberculin in right eye. Reaction, O.

CASE XVIII. L. M., female, aged thirty-five years. Clinical diagnosis: Necrotic granuloma (folliclis). No evidence of other tuberculous lesion. April 13, 1908, one per cent. tuberculin in right eye. Reaction, +.

CASE XIX. R. G., female, aged twenty-three years. Clinical diagnosis: Necrotic granuloma (folliclis). This patient, several years ago, suffered from an attack of erythema indurata (Bazin) and now has enlarged cervical glands, which probably are tuberculous. April 17, 1908, one per cent. tuberculin in right eye. Reaction, +.

CASE XX. H. H., female, aged twenty years. Clinical diagnosis: Necrotic granuloma (folliclis). No evidence of other tuberculous lesion. April 13, 1908, one per cent. tuberculin in right eye. Reaction, + +.

CASE XXI. N. M., female, aged fifteen years. Clinical diagnosis: Lupus vulgaris. No evidence of other tuberculous lesion except slight dullness and diminution of the breath sounds at the apex of the right lung. April 13, 1908, one per cent. tuberculin in right eye. Reaction, +.

CASE XXII. B. M., female, aged thirty-three years. Clinical diagnosis: Lupus vulgaris. No evidence of other tuberculous lesion. March 26, 1908, one per cent. tuberculin in right eye. Reaction, +.

CASE XXIII. G. M., male, aged thirty-one years. Clinical diagnosis: Lupus vulgaris. No evidence of other tuberculous lesion. February 18, 1908, one per cent. tuberculin in right eye. Reaction, + +.

CASE XXIV. K. K., female, aged thirty-six years. Clinical diagnosis: Lupus erythematosus. No evidence of tuberculous lesion. February 28, 1908, one per cent. tuberculin in right eye. Reaction, O. April 20, 1908, one per cent. tuberculin in left eye. Reaction, O.

CASE XXV. E. G., male, aged twenty-six years. Clinical diagnosis: Lepra. No evidence of any tuberculous lesion. April 17, 1908, one per cent. tuberculin in right eye. Reaction, O. April 23, 1908, one per cent. tuberculin in left eye. Reaction, O. This patient was tested as a matter of interest, since it is known that in leprosy injections of tuberculin under the skin may be followed by a constitutional reaction.

Since the ophthalmic test may be positive in typhoid fever it may be well to state that none of the patients who exhibited a positive reaction had suffered from a recent attack of this disease.

Summary: In summarizing the results it seems best to deal with the dermatological cases separately. Of the other patients, in all those in whom the diagnosis was assured, either by the presence of distinct physical signs or by the demonstration of the presence of the tubercle bacillus in the sputum, a positive reaction was obtained, although in some instances two or more trials were necessary. The two patients (Cases XIV and XV) in whom a tentative diagnosis of pulmonary tuberculosis was made reacted negatively; the control cases (XVI and XVII) also gave negative results.

Of the dermatological cases, in all those, six in number, in whom the affection was one of tuberculous nature—for while necrotic granuloma is not of itself a tuberculous lesion according to the dermatologists, it seems to bear a constant relation to tuberculosis—an undoubted positive reaction was obtained, while in the case of erythematous lupus (XXIV), the reaction was negative.

Conclusions: If one can deduce conclusions of value from the results obtained in so few cases, it would seem that the following might be justifiable:

1. The ophthalmic test is an aid of some value in the diagnosis of tuberculous conditions of the lungs, but in many instances is unnecessary, since the diagnosis may be assured by the examination of the sputum and by physical examination of the chest. However, in incipient cases with equivocal signs, the test may be of distinct assistance, provided its results can be relied upon. Whether reliance is to be placed upon it or not further study of the reaction will show.

2. In lupus vulgaris and tuberculides of the type of necrotic granuloma (folliclis), the ophthalmic reaction seems to afford a very material help in the diagnosis of the condition.

The writer wishes to express his sincere thanks to Dr. F. P. Kinnicut, attending physician to the Presbyterian Hospital; to Dr. E. F. DuBois, of the interne staff of the Hospital; to Dr. F. J. Parker, ophthalmologist; and to Dr. Jerome Kingsbury, dermatologist to the dispensary, as well as to his other associates of the dispensary staff, whose aid and interest have made possible the writing of this paper.

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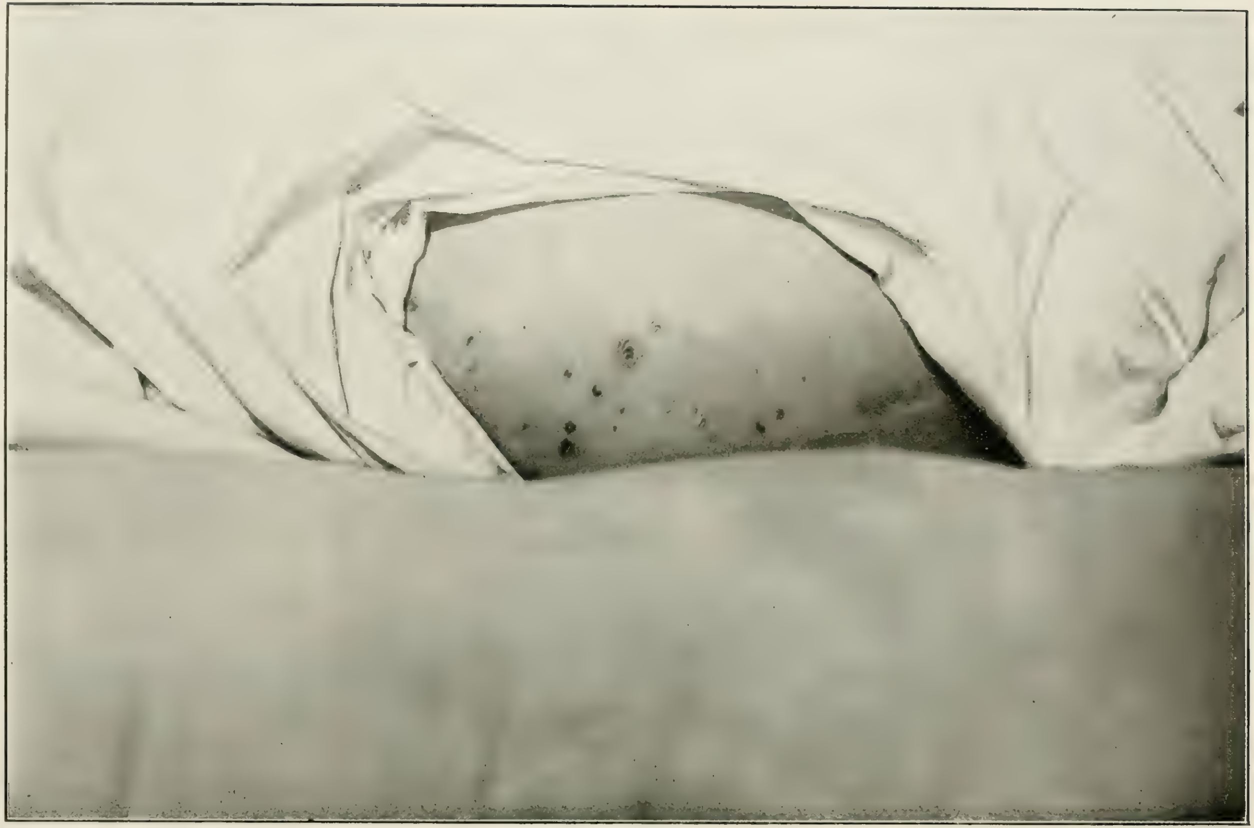


FIG. 1—ERUPTION OF MENINGOCOCCUS SEPTICAEMIA

VIEW OF LEFT HIP, SHOWING THE NECROTIC AREAS IN CENTERS OF SPOTS

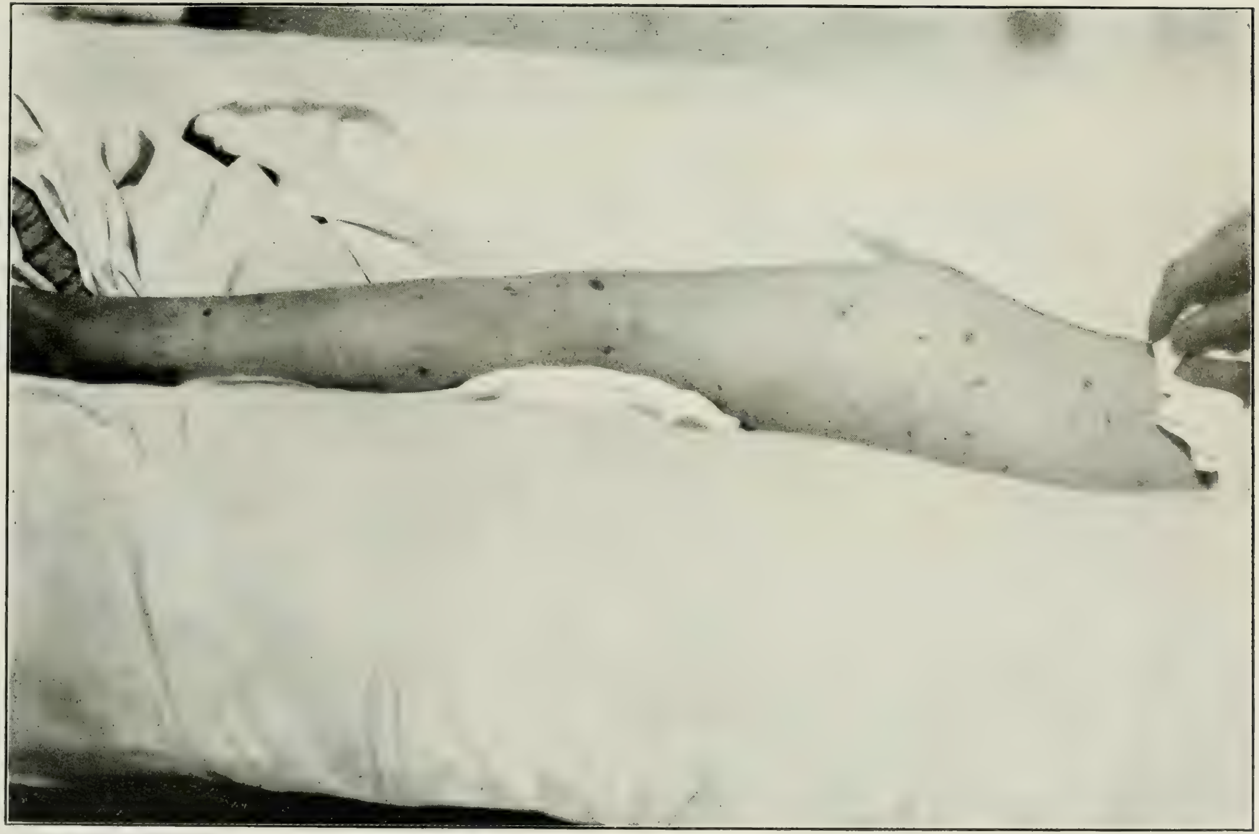


FIG. 2—VIEW OF LEFT LEG, SHOWING ERUPTION OF MENINGOCOCCUS SEPTICAEMIA

XXIV.

MENINGOCOCCUS SEPTICÆMIA, WITH STERILE CEREBRO-SPINAL FLUID.

By David Bovaird, Jr., M.D., Associate Physician.

(FROM THE SERVICE OF DR. F. P. KINNICUTT.)

The specific relation of the diplococcus of Weichselbaum to epidemic cerebro-spinal meningitis is established beyond question. Investigations of the last few years have aimed to solve the mystery as to the sources of infection and the route taken by the invading organism in reaching its objective point in the meninges of the brain and spinal cord. The first light on these questions came from the discovery by Albrecht and Ghon[15] that organisms apparently identical with the diplococcus of Weichselbaum could be found in the nasal secretions of some of the patients. This observation was quickly followed by many others. Thus, Flügge[16] found the meningococcus in the nasal secretion four times in 44 trials, and von Lingelsheim[17] 182 times in 787 examinations, and Koplik[18] quotes Goodwin and Sholly to the effect that the organism can be obtained from the nasal mucus in fifty per cent. of the patients during the first two weeks of the disease, and in ten per cent. of those who come in contact with the patients. It seems, therefore, established that the respiratory tract, especially the nasal fossæ, is the usual avenue of entrance for the organism. The route by which the bacteria make their way from this outpost into the cranial cavity has been the subject of speculation. The popular theory has been that the meningococcus made its way directly through the sphenoidal or ethmoidal sinuses to the base of the brain. The facts, so far as they are at present known, lend support to that theory. Evidence is, however, accumulating that it is possible that a general meningococcus septicæmia may occur in the absence of a meningitis, and that the systemic circulation may, in some cases at least, be the pathway by which the organism reaches and lodges in the meninges.

That the meningococcus may be found in the blood in certain cases of epidemic cerebro-spinal meningitis has been known for some time. In a recently published article Duval[1] reports such a finding, and has collected from the literature a number of others. The first positive blood finding is credited to Gwyn, in a patient of Osler.[6] Warfield and Walker have reported one case, Lenhartz two, Robinson one in six cases examined, Möller one, Martin and Rhode one, and Elser, in 41 cases of cerebro-spinal meningitis, found the specific coccus in the blood in ten. On the other hand Bettencourt and Franca[11] report six cases in which the blood examination during life was negative, and three in which the organism was found in the heart-blood, while Councilman, Mallory and Wright in 35 cases made cultures from the heart-blood with negative results. Flügge[12] and Rautenberg[13] each report failures to cultivate the meningococcus from the blood.

In addition to these reports collected by Duval, the writer has been able to find two positive findings made by Cochez and Lemaire,[2] two by Jacobitz,[3] and one by Jäger.[4]

In a number of other cases the specific coccus has been found in locations indicating a systemic infection. Thus, Fronz[5] found the organism in the meningeal exudate and in the right ankle, and Osler[6] some years ago reported a similar observation. Gradwohl,[7] in a post-mortem examination of a pregnant woman who had died on the third day of her illness, found the meningococcus in the meninges of both the patient and the seven months fetus, and also in pus from the mother's ear, although cultures from the lungs, blood, placenta, and uterus were negative. Jäger[4] reports finding the organism in the urine in one case during life.

A general distribution of the organism throughout the body is reported by two observers. Jäger found it in the pericardium, pleural exudate, liver, spleen, and pus in the pelvis of the kidney in one case, and Duval isolated it from the eye, pericardium, heart's blood, meninges, and cerebro-spinal fluid. Wintersteiner and Tooke (see Duval) each recovered the organism from the spinal fluid and found it present in smears from the eyes, in which iridocyclitis was present, but could not obtain it in cultures from the latter site. Von Drigalski[14] cultivated the organism from herpetic vesicles on the ear, although he could not obtain it from the blood of the patient.

It thus appears that in a certain number of cases of cerebrospinal meningitis the meningococcus may be found not only in the spinal fluid, but in the blood, or in various sites which indicate systemic infection. However, the number of such systemic infections thus far recorded is small, and we must regard them as rare. Duval, summing up his study, notes this fact, and adds that there is at present no authentic case on record in which the meningococcus has produced lesions outside the meninges in the absence of a pre-existing meningitis.

In 1902, however, Salomon[8] reported the following case: The patient, a laborer's wife, 32 years of age, was seized on July 30, 1901, with pains and swellings in her hands, elbows, and knees. On the following day she had a chill, followed by fever, and an eruption on the hands and feet, and became weak and faint. She was admitted to hospital on the 3rd of August. She was then suffering from a high fever, and the constitutional symptoms of a severe infection without focal signs, and had a profuse eruption resembling erythema exudativum. The fever and other symptoms persisted. On August 7th a blood culture yielded the meningococcus. From this time on there was no radical change in her condition, the fever continuing, and new crops of the eruption appearing from time to time, until the end of September, when she developed signs of a meningitis, and lumbar puncture gave vent to a characteristic turbid fluid containing meningococci. The patient finally recovered in December. She had been sick for two months before the advent of the meningitis, and the meningococcus had been found in the blood nearly two months before the lumbar puncture, but as there is no record of a lumbar puncture having been made before the development of the symptoms of meningitis, the possibility of the presence of a meningitis early in the disease is not excluded in this case.

The following case, reported in October of this year by Liebermeister,[9] is free from that objection: A laborer, 59 years of age, was admitted to hospital February 25, 1908, complaining only of pain and stiffness in both shoulders. The beginning of his trouble he could not definitely place. The patient showed a high fever with signs of severe infection, but no focal symptoms. There was a roseola resembling that of typhoid. On March 1st a blood culture yielded organisms later proven to be Weichselbaum's diplococcus. On the 7th of March lumbar puncture gave a clear fluid, under normal pressure, and containing no sediment. On the 18th, 20th, and 31st of March cultures from the blood still gave meningococci. On the 8th and 18th of April further cultures were negative. During all this time the fever of septic type continued, the eruption developed in repeated crops, and the patient had pains about various joints and some rigidity of the extremities. He had, however, no rigidity of the neck, no Kernig, no signs of involvement of the cranial nerves, so that there appears no good reason for assuming that he had meningitis, especially in view of the negative results of the lumbar punctures (2). In May the patient developed an abscess on one arm, in which the common pyogenic organisms were found, no meningococci. Finally the fever gradually subsided, the general condition improved and the patient recovered toward the end of June. In view of the evidence this case must, it seems, be accepted as a meningococcus septicæmia without meningitis. As will later appear, we do not record this as proven by the negative results of the lumbar puncture alone, but the absence of the clinical signs of meningitis during the many weeks of observation, and the normal spinal fluid, constitute as strong evidence as can be had, so long as the patient recovers.

Andrewes,[10] pathologist of St. Bartholomew's in 1906, reported the following decisive experience: A physician, 52 years of age, was suddenly taken sick on the morning of February 12th, 1906. A few spots appeared on the face at noon. By evening a profuse hemorrhagic purpura had developed. The patient was moribund, temperature 99.4°, pulse imperceptible, respiration 34. Intracellular cocci found in the polynuclear leucocytes of the blood were proven by cultural studies and pathogenicity to be the diplococcus intracellularis.

The autopsy showed no meningitis either in the gross or microscopically. Extravasated meningeal blood, however, yielded a more abundant growth of the diplococci than did that of the heart.

Andrewes concluded that the case was proven to be one of blood infection by the meningococcus without meningitis.

In view of this evidence of the possibility of systemic infection by the meningococcus in the absence of meningitis, we wish to put on record the following case:

S. P., aet. 15 years. Russo-American. Admitted October 5th, 1908.

Family History: Irrelevant. No contagious disease in neighborhood; no meningitis among her friends. Personal: Born in New York, lives under fair tenement house conditions. Menstrual: Patient has never menstruated. Past History: From birth up to two years she had frequent hemorrhages from the navel. Since then she has enjoyed good health. No previous illness except measles eight years ago, uncomplicated. No history of hemophilia, scurvy or lues.

Present History: Yesterday she was perfectly well. She went to a holiday dinner and is said to have greatly overeaten. About midnight she vomited three or four times. The vomitus consisted of green undigested food. The rest of the night she seemed to sleep quietly. This morning she complained of slight headache. The child did not seem very ill and the parents went to the Synagogue leaving the child at home alone. This noon, when they returned, the child seemed as if dead, her face was yellow, and there were many dark spots on the body. She did not recognize her parents; her urine and feces were passed involuntarily. Since then she has been in a stupor, has shaken a little but has had no real convulsions. There has been no vomiting, and she can swallow a little. The eyes have been closed. She was brought to the Hospital in ambulance.

A careful physical examination was made by Dr. DuBois. Only the important findings are here reported.

Patient is a well nourished, but rather undersized girl of fifteen. She lies doubled up on her right side in stupor, but she can be roused enough to give her name and age. When let alone she is perfectly quiet, when disturbed she resists a little with her hands. She is cyanotic, not anæmic or dyspnœic. She looks very seriously ill.

Tongue: Moist and coated with white fur and covered with thick mucus.

Eyes: Pupils small, equal, react slightly; no ocular palsies, no nystagmus. On the ocular and palpebral conjunctiva are several small petechial spots.

Neck: Not stiff; when moved forward of the median line, patient arouses and resists a little.

Heart: No enlargement. Action, 140 to the minute, regular, of good force. No murmurs heard.

Pulses: Equal, correspond to apex, small, soft, walls of vessel not felt. The other viscera apparently normal.

Extremities: Upper, no paralysis.

Extremities: Lower, no paralysis. No œdema, knee jerks normal, no Babinski. Kernig: There is slight resistance when leg is fully extended on the flexed thigh.

Surface: Over the whole surface, but most abundant on the abdomen is a profuse eruption of irregular purpuric (purple) spots varying in size from pin point to 2 c.m. in diameter. They occur in the face, conjunctivæ and pharynx.

Clinical Diagnosis: Epidemic Cerebro-spinal Meningitis, Fulminant.

October 7th: Temperature 100°–101°. Lumbar puncture at 9 P. M. October 5th, withdrew normal fluid under normal pressure. High leucocytosis. Urine normal. Patient has been very noisy and irrational, at times abnormally bright. She seems somewhat hysterical. She can repeat her multiplication tables with few mistakes. Neck seems a little stiff.

Surface: No new spots have appeared, the old ones are a little darker and are now a reddish purple, edges indistinctly defined, many of them have gray centers which seem to be on the point of sloughing. These are slightly raised and distinctly tender. There are about twenty such spots on the buttocks, three on right hand, one on chin, one on left shoulder, about twenty on the thighs and legs. There is a crop of herpes on the lips.

October 9th: Patient is a little quieter, she is obstreperous but perfectly rational. She has no headache. The herpes vesicles on the lips are more marked. Tongue slightly coated and red at the edges. The petechial spots on soft palate are now white and sloughing. The right eye shows a severe conjunctivitis, the whole conjunctivæ being intensely injected and swollen. The left conjunctiva is normal. Hearing is acute. Neck is a little stiff. Joints held somewhat stiff but not tender. Kernig: Patient complains of great pain when attempt is made to extend leg beyond 135°.

No new petechial spots have appeared. The spots which two days ago showed gray centers are indurated and tender, not broken down and seem to be dissolving. Lumbar puncture yesterday was unsuccessful, only blood being obtained after several punctures.

October 11th: Temperature has risen somewhat. Patient has been quieter, is perfectly rational. She has had pain in feet and abdomen. Lumbar puncture withdrew only a small amount of dark clotted blood. Conjunctivitis in right eye has increased rapidly. Yesterday it was found that cornea was hazy, iris blurred and markings indistinct, and that the anterior chamber contained much yellowish exudate. The eye was examined by Dr. F. J. Parker, who made the diagnosis of hemorrhage in the eye with iridocyclitis. To-day there is no facial paralysis, hearing is acute, there is no headache, neck is stiff and cannot be bent beyond the midline. Mouth shows two small ulcers where the petechial spots are located.

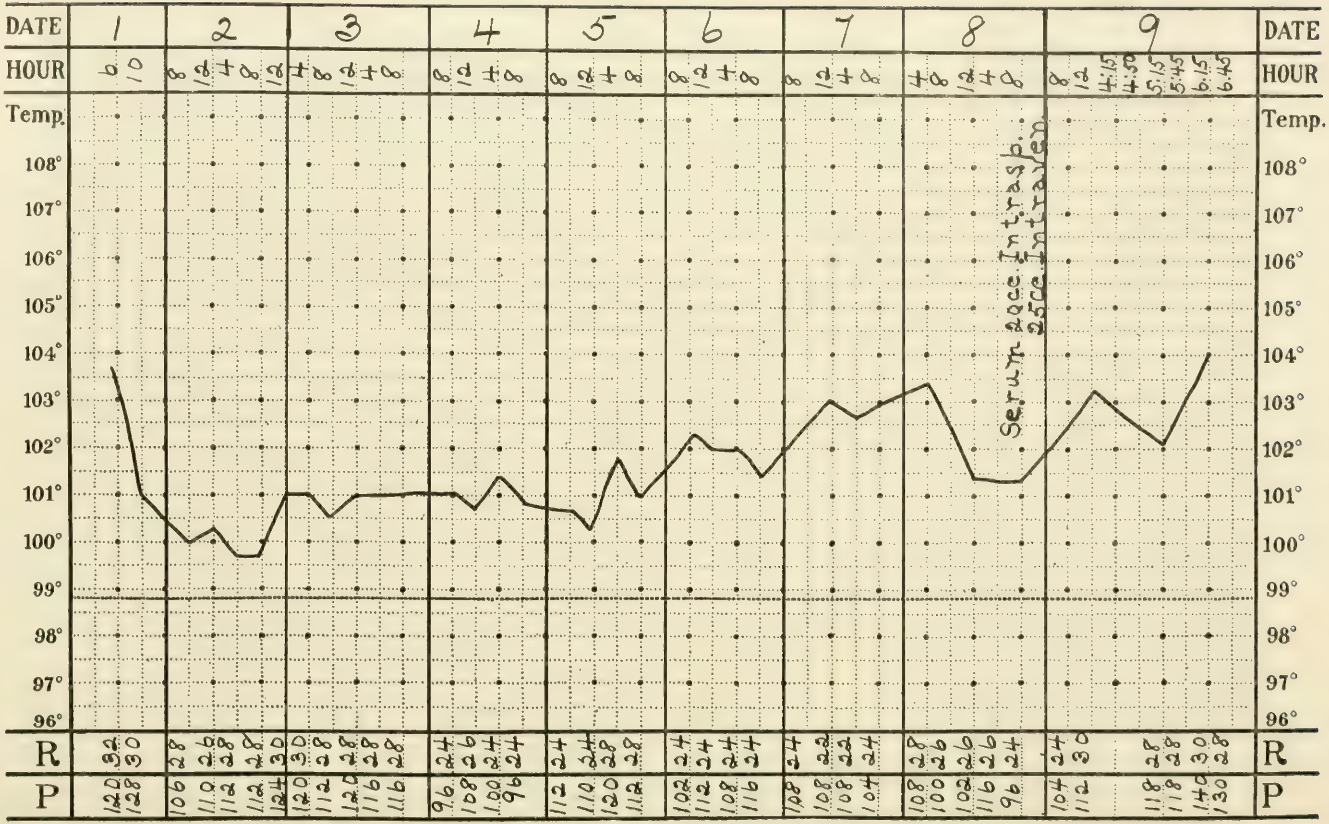
Feet: Over outer aspect of each ankle there is rednesss, slight tenderness, increased local heat. The right foot is the more tender.

Surface: All the smaller purpuric spots have almost disappeared and there are now only faint purplish mottlings. A few of the larger ones are still indurated with gray sloughing centers. The skin is not broken down over any of them. All the joints are stiff and a little painful on movement.

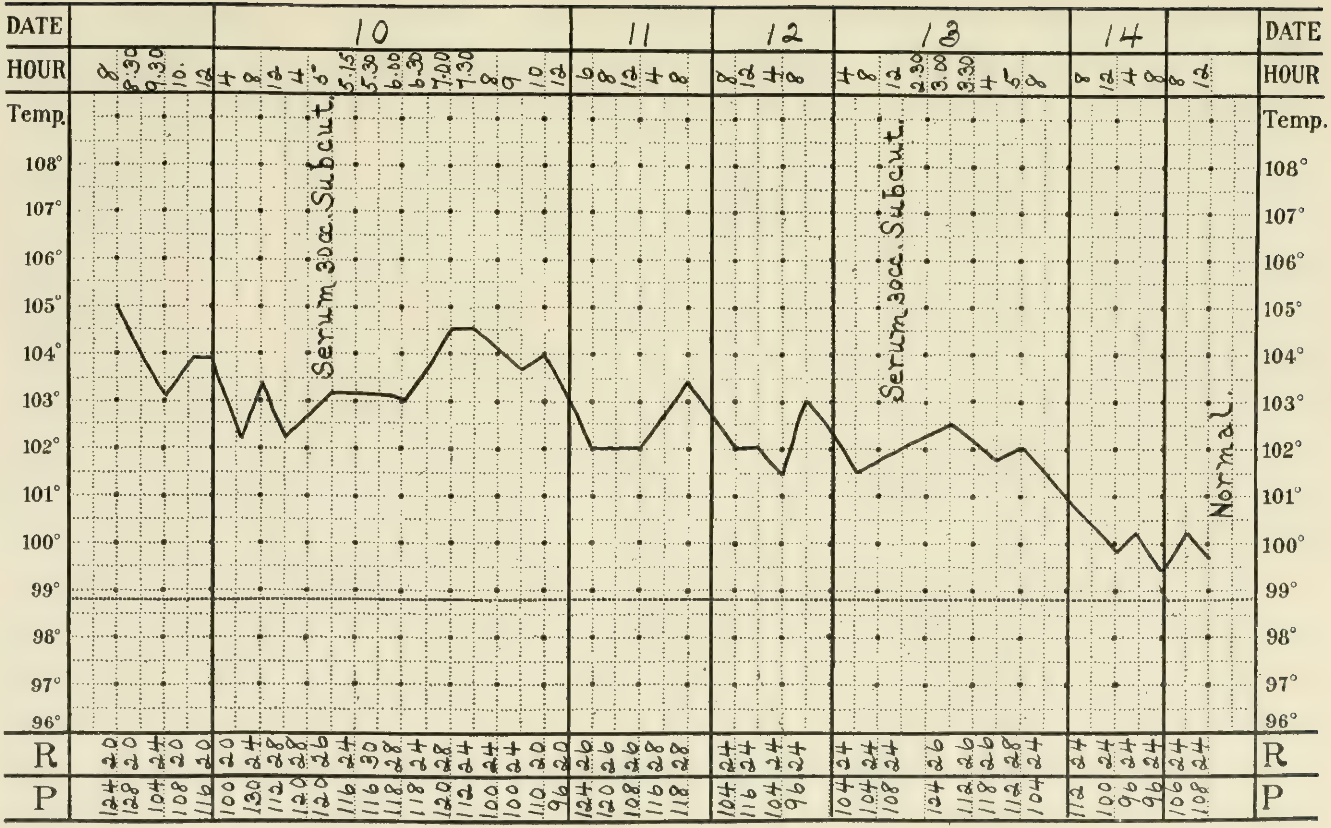
October 13th: Temperature 101°–103°. Meningococci have been found in the blood culture taken October 9th. Patient is very noisy and at times irrational. Whole anterior chamber of eye is hazy, exudate does not seem increased; conjunctivæ not so much inflamed. Neck is very stiff. Spots are fading, there are now about fifty left. A few contain pus, none are broken down. Kernig: Legs can be extended to within 45° of straight line. Knee jerks faint. Feet no longer swollen. General condition not so good. The cultures obtained from the blood were submitted to Dr. Flexner who corroborated the diagnosis.

October 14th: On October 13th lumbar puncture, one space higher than where last attempted, withdrew about 20 c.c. of claret colored fluid not under increased pressure. It did not look purulent and no organisms were found. 20 c.c. of Flexner's meningitis serum were injected into spinal canal and 25 c.c. more were given in an intravenous infusion just after a blood culture had been made (N. B.—This latter proved sterile). Following this the temperature rose to 104.6° but has fallen a little, being 103.4° this A. M. She is still very noisy. She does not seem irrational and can multiply 6 x 6 and 5 x 8 correctly. She seems hyperesthetic when touched. Neck not quite so stiff as yesterday. Throat clear except for white patches on left tonsil and right cheek where petechial patches were located. Right eye: Conjunctival sac deeply injected and swollen, although not so much as three days ago. Cornea is cloudy, pupil moderately dilated, iris cloudy. There is a white patch apparently in middle of anterior chamber. Knee jerks active. No Babinski. Sensation: Patient can distinguish accurately between sharp and blunt end of a pin. Kernig: Right leg can be extended to within 35° of a straight line. Left can be extended to almost a straight line. Joints are no longer stiff. Feet only a little tender. No paralysis, eyes look in every direction, tongue does not deviate. General condition a little better. Ear drums normal.

October 19th: This is the fifteenth day since the onset. Patient is improving steadily. On October 17th 30 c.c. of Flexner's serum were given subcu-



Temperature Chart of a Case of Meningococcus Septicæmia.


DATE
HOUR
Temp.
108°
107°
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
R
P
10
11
12
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14
8 8.30 9.30 10. 12
4 8 12 4 5 5.15 5.30 6.00 6.30 7.00 7.30 8 9 10 12
6 8 12 4 8
8 12 4 8
4 8 12 2.30 3.00 3.30 4 5 8
8 12 4 8
8 12
Serum 30x. Subcut.
Serum 30x. Subcut.
Normal.
20 20 24 20 20 20 24 28 28 26 24 30 28 24 28 24 24 24 20 20 26 26 26 28 28 24 24 24 24 24 24 24 26 26 26 28 24 24 24 24 24 24 24
124 128 104 108 116 100 130 112 120 120 116 116 118 118 120 112 100 100 110 96 124 120 108 116 118 104 116 104 96 104 104 108 124 112 118 112 104 112 100 96 96 106 108

taneously. Since then the temperature has fallen from 101.5° to 100°. The leucocytes are decreasing. The patient is very noisy and irrational at times, but this seems to be largely hysterical. This morning she is rational and laughs and complains of no pain. The eye is still hazy and there is an opacity apparently on the anterior surface of the lens, but this is decreasing in size. The pupil is dilated and a little irregular. The conjunctivitis is less marked.

October 20th: Lumbar puncture gave clear fluid at first, later a little blood; pressure was low, fluid rose in tube to 11 c.m., and when patient was crying ranged between 11 and 27 c.m., returning to 11 c.m. when patient became quiet.

October 30th: Temperature 99° to 100.° Patient eats better, sleeps well, is perfectly rational. She cannot do the multiplication table as well as the first week of her illness. She has no pain, no headache. Her complexion is pale with a slight greenish tint. Neck is no longer stiff. Kernig: Legs can be extended to straight line but this seems to hurt patient. Right eye: tension very low, conjunctivæ less inflamed, pupil dilated, iris a little less cloudy. General condition improving.

November 5th: Temperature remains below 100.° Patient is up in chair without fatigue. She has no headache, no earache, no pain in the eye. Vision with left eye seems normal, with right eye is lost. Intraocular tension very low, pupil dilated and a little irregular. Far back in the posterior chamber is a gray mass. Iris is dull, conjunctivæ slightly injected. Sloughs on tonsils and inside of cheeks have entirely healed.

November 25th: The patient has made a steady improvement and is now able to be up and about. The right eye is still blind. Beyond a moderate anæmia she shows no other consequence of her illness.

Table of Leucocyte Counts, Lumbar Punctures, Etc.

Date	Day of Disease	Leucocytes	Hour	
Oct. 5	1		12:30 a.m.	Onset with vomiting.
" 5	1		9 a.m.	Lumbar Puncture—clear fluid
" 6	2	27,500		
" 8	2	28,600	5:20 p.m.	Lumbar Puncture, small amount of blood.
" 9	5		3 p.m.	Lumbar Puncture, dark blood clot.
" 9	5		5:20 p.m.	Blood Culture, Pure culture meningococci.
" 12	8	19,400		
" 13	9		4 p.m.	Lumbar Puncture, Clear blood-tinged fld.
			4:15 p.m.	Flexner's serum, 20 c.c. Intradurally.
			4:30 p.m.	Blood Culture—Sterile.
			4:50 p.m.	Flexner's serum, 25 c.c. Intravenously.
" 14	10	18,000	5:15 p.m.	Flexner's serum, 30 c.c. Subcutaneously.
		18,200		
" 15	11	18,400		
" 16	12	13,800		
" 17	13	13,100	2:30 p.m.	Flexner's serum, 30 c.c. Subcutaneously.
" 18	14	13,000		
" 19	15	9,000		
" 20	16	11,100	6:25 p.m.	Lumbar Puncture—Clear Fluid.
" 21	17	10,400		
" 22	18	9,800		
" 24	20	10,100		
" 26	22	23,500		
" 27	23	17,600		
" 30	26	14,100		
Nov. 2	29	14,700		

Differential Counts of Leucocytes.

Daily Percentages:

	Oct 6.	Oct. 12	Oct. 14	Oct. 17	Oct. 27
Polynuclears	82.	72.7	61.3	78.*	64.
Transitionals	3.7	2.7	.2	2.3	1.3
Large Mononuclears	8.	9.6			
Lymphocytes	6.	15.	27.8	19.	34.
Basophiles	.3	0.	1.	0.7	0.
Eosinophiles	0.	0.	.7	0.7	7.
Platelets	few	few	few	few	few

* 300 leucocytes counted.

PATHOLOGICAL REPORTS.

October 9—Blood culture on broth: Pure culture of meningococcus—*Cecil.*

October 13—Blood culture on broth: Both sterile.

October 12—Smears from right conjunctiva: Pus and fibrin. Very few micro-organisms—*Meakins.*

October 11—Culture from right eye (blood agar): Smears show mucus, pus, Gram: cocci and bacilli. Cultures give staphyloccus albus and B. Xerosis.—*Cecil.*

October 13—Smears and cultures from purpuric spot (sheep serum agar): Smears show a few scattered pus cells but no bacteria. Cultures sterile—*Cecil.*

October 5—Spinal fluid: 20 c.c. perfectly clear, colorless fluid. No sediment. No coagulum. Smears negative. Culture sterile—*Cecil.*

October 9—Spinal fluid: About 1 c.c. of serum containing a large blood clot. Smears show blood but no pus. No micro-organisms. Cultures sterile—*Cecil.*

October 13—Spinal fluid: 15 c.c. of blood tinged fluid. Dark red sediment. Smears show blood but no pus. Cultures sterile—*Cecil.*

October 20—Spinal fluid: 25 c.c. blood tinged. Dark red coagulum. Smears show blood, no pus, no bacteria. Cultures sterile—*Cecil.*

October 20—Spinal fluid: 30 c.c. of clear colorless fluid. No coagulum. No sediment. Smears entirely negative. Cultures sterile—*Cecil.*

October 7—Urine, 24 hours. Alkaline Sp. gr. 1014. No Albumen, No Sugar. No indican.: Quantity 1076 c.c. Uric Acid .403 gms. Total Phosphates, 2.09 gms.—*Granat.*

As it is established that meningococcus septicæmia is possible, without meningitis, the question naturally arises whether the case here recorded belongs in that category.

On the admission of the patient the clinical diagnosis was entered as cerebro-spinal meningitis. In the light of the negative lumbar puncture, and the marked hemorrhagic symptoms, together with the absence of conclusive signs of meningitis, purpura hemorrhagica was later suggested. We are not yet entirely satisfied as to the presence of meningitis. On admission the patient was stuporus, but without notable stiffness of the neck or extremities, or other definite evidence of invasion of the cord or brain. Later the stupor gave place to a fretful and irritable mental condition, in which the patient appears to have been more acute than since her recovery, with definite rigidity of the neck, Kernig's sign, and general hyperesthesia. The apparent

Kernig may have been due to the involvement of the knee joints. Rigidity of the neck is seen, as all know, in conditions free from meningitis, such as typhoid fever or pneumonia, and Kernig's sign is not by any means limited to meningitis, but taken together these symptoms certainly point to a definite involvement of the cord. On the other hand, five successive lumbar punctures yielded a quantity of cerebro-spinal fluid which must have shown the meningococcus if the cord had been involved in the inflammatory process, but which on each occasion proved sterile.

The chief source of cerebro-spinal fluid, it is agreed, is the choroid plexus. The maintenance of a normal supply of the fluid about the cord implies an uninterrupted circulation of the fluid from the ventricles of the brain through the foramen of Magendie to the spinal canal. The quantities of fluid obtained at lumbar puncture, 20 c.c., 1 c.c., 15 c.c., 25 c.c., and 30 c.c. seem to clearly show that there was no obstruction to the normal course of the fluid, or the later tappings would have been "dry." The inability to obtain more than 1 c.c. on the second puncture was evidently due to the presence of considerable blood at the usual point of puncture. When the needle was later inserted in a higher space the larger quantities were readily obtained. The normal pressure reading obtained at the puncture of October 20th, is another strong argument for the presence of normal circulatory conditions in the spinal canal. Involvement of the cord can therefore, it would seem, be excluded.

The possibility remains that there was a meningitis limited to a part, or the whole of the cerebral surface, but cut off from connection with the surface of the cord or of such nature that the usual purulent exudate was lacking. For either of these suppositions no support can be found in the pathology of cerebro-spinal meningitis. Involvement of the cord seems always to be found. In the thirty-five autopsies of Councilman, Mallory and Wright the process always invaded the surface of the cord to some extent, and so far as the writer can learn, such extention of the disease is constant. It is well known that in the early stages of meningitis the pathologic process may be limited to a congestion of the pia-arachnoid, with very little exudation, so that an early lumbar puncture may be negative, but in cases protracted for two weeks or more the typical exudate always appears and the spinal fluid sooner or later shows pus and cocci. It is also true that in a series of punctures one or more may be sterile, while the others yield the specific organism, but the writer can find no reference to an experience such as ours, in the presence of a definite meningitis.

The involvement of the eye to the extent described may be regarded as good evidence of the presence of a meningitis. Councilman, Mallory and Wright report the histological examination of two eyes presenting the lesions of iridocyclitis as a complication of cerebro-spinal meningitis. In one of these they were able to trace the meningococci along the optic sheaths from the brain to the eye, apparently showing that the inflammation of the eye developed by direct extension from the pia-arachnoid. On the other hand, it must be granted that, the organism being present in the blood, it may readily lodge in any part of the body, affecting the eye quite as easily as the joints.

In view of the conflict of evidence it is impossible to reach an entirely satisfactory conclusion, but it seems easier to explain the clinical symptoms as expressions of a general bacteriemia, than to assume the presence of a meningitis in the face of the strong evidence against it. In the title of this report, we have, however, stated only the facts, a meningococcus septicæmia with sterile cerebro-spinal fluid.

Apart from the difficult problem of diagnosis the case here reported presents some interesting features.

The eruption was a very remarkable one in the size of the petechial areas and the sloughing which took place in the centers of the larger patches. The accompanying photographs suggest the number and size of the spots and in some instances the central sloughs are faintly shown.

In Salomon's, and Liebermeister's patients also, the eruptions were striking features of the illness. They describe the lesions as a roseola, resembling that of typhoid, or like flea bites. The multiform character of the eruptions seen in cerebro-spinal meningitis is too well known to merit comment. It is, perhaps, suggestive that in these cases, as in our own, the eruptions were so marked, the meningococcus being present in the blood. Is the eruption in these cases the expression of an embolic or thrombotic process set up by the lodgment of the specific organism in the capillaries of the skin?

It is of interest that in Andrewes' patient, and in our own, the eruption marked the onset of the disease, and if we take this view of its pathogenesis, we have another argument for primary blood infection in our case.

The photographs of the eruption here shown closely resemble those of a case of meningitis described by L. R. Williams in Vol. V (1902) of these Reports.

Liebermeister notes that his case enables us to determine the accessory symptoms of meningitis, that is, those due to the general infection and not to the focal lesion, and he enumerates these as hectic fever, pain in the joints, and contractions of muscles, slight mental dullness, emaciation, and a roseola-like rash. The fever, eruption and arthritis, with resulting muscular contractions, are all found in Salomon's case, as well as the one here reported.

All but two of the ten cases in which Elser found the meningococcus in the blood, proved fatal, and in almost all the other cases of meningococcus septicæmia here mentioned the outcome was the same. It is, therefore, notable that our patient made a prompt recovery; Liebermeister's was in hospital for four months; Salomon's for more than that period. The patient here reported was quite well at the end of one month, and is now, at the end of the second, able to return home at any time she wishes. In fact, whether she had meningitis or not the rapidity of her recovery was remarkable, all the more so if we grant that she had meningitis as well as the blood infection. To what degree this rapidity of recovery was determined by the energetic administration of the Flexner serum, we cannot say, but from clinical observation we were satisfied that the serum played an important part in the improvement of the patient.

It has been noted that the blood culture taken immediately before the first dose of serum, as well as those made later, proved sterile, but it would not do to assume from this fact that the organisms had altogether disappeared from the blood before the introduction of the serum. The efficacy of the serum has been too well proven in cases of meningitis to make it desirable to pursue this point further.

Special mention must, finally, be made of the ocular complication. Beginning as a conjunctivitis, this quickly developed into a panophthalmitis, with hemorrhage in the vitreous humor. The affection increased rapidly and seemed to threaten the complete destruction of the eye. Following the use of the serum improvement began, which, in Dr. Parker's opinion, was most remarkable. From that time on the condition changed rapidly for the better, and the preservation of the eye, though without vision, seems assured. Dr. Parker considered the affection as typical of metastatic infective inflammation of the eye.

The cases of Tooke, Wintersteiner, and Duval, were apparently of like kind. It is notable that these were all fatal cases. The complication is not a frequent one, and the cases just mentioned are the only ones in which Duval could find mention made of it. Koplik speaks of it as a complication of fatal cases only. The fortunate outcome for our patient is, therefore, all the more noteworthy, and constitutes a strong argument for the efficacy of the serum.

The cases here grouped together fairly establish the possibility of a primary meningococcus septicæmia, and suggest the clinical picture.

Doubtless, with more frequent bacteriological study of the blood during life, we shall find such cases not very uncommon.

My thanks are due Dr. Kinnicutt for the privilege of reporting this case, and also to the house physician, Dr. DuBois, for the very careful clinical notes recorded from day to day.

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THE BRIDDON MEDAL.

CONDITIONS OF AWARD.

1. This medal shall be known as the Briddon Medal.

2. This medal shall be awarded once in two years to that member of the Society of the Alumni of the Presbyterian Hospital who shall present the most meritorious essay on a medical, surgical, pathological, or bacteriological subject.

3. The award of this medal shall be made by a committee of three, consisting of the President, together with a member of the medical and surgical staffs of the Medical Board of the Hospital to be appointed by the President at the annual May meeting.

4. All essays shall be typewritten and forwarded to the Superintendent of the Hospital, on or before October 1 prior to the award of the medal.

5. Each essay must be signed by some fictitious name or device and must be accompanied by a sealed envelope containing this name or device together with the true name of the writer.

6. If, in the judgment of the committee, none of the competing essays is sufficiently meritorious, no medal shall be awarded; in such event the sum ordinarily expended for the purchase of such medal shall be used for the purchase of standard medical works, to serve as a reference library for the house staff of the Hospital.

7. The medal shall not be awarded a second time to any member of the Society.

8. No member of the Medical Board shall compete for this medal.

9. The successful essay shall be published in the first number of the Presbyterian Hospital "Medical and Surgical Report" issued after the award of the medal.

10. No essay shall be submitted a second time in competition for this medal.

11. The first award of this medal shall be made in December, 1903, by the President of the Medical Board at the annual dinner of the Society.

NOTE.—Prize Essay will be found on page 139.

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Presbyterian Hospital in the City of New York
Medical and surgical report

GERSTS